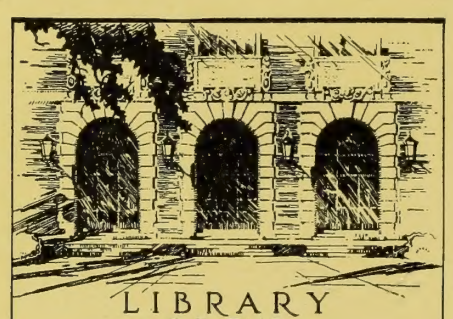

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PSYCHOPHARMACOLOGY ABSTRACTS

Vol. 3 No. 1

U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
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PSYCHOPHARMACOLOGY ABSTRACTS

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REVIEWS, SUMMARIES, BIBLIOGRAPHIES, AND GENERAL ARTICLES AND BOOKS

1 Dunham, Richard M., & Howard, K. An effect of research training in the study of psychiatric drug treatment. American Journal of Psychiatry, 1963, 119, 748-753.

Analysis of 1957 and 1960 articles in six psychiatric journals on chemotherapy research indicate the desirability of collaboration between physicians and persons trained in scientific research. The articles were evaluated on the basis of 28 items concerned with the adequacy of reporting and methodology. The poorest scores were those of physicians working in private practice, medical schools and state hospitals. Articles prepared in collaboration with a Ph.D. contained the most methodological features considered desirable. The data support the use of interdisciplinary teams in psychopharmacological research.

NASA-Manned Spacecraft Center, Langley Field, Va.

2 Prange, Arthur J., Jr. Recent advances in therapeutics: Psychoactive drugs. North Carolina Medical Journal, 1963, 24, 63-66.

Psychoactive drugs have increased the need for clinical judgment, experience, and caution. Side effects of tranquilizers such as Stelazine, Thorazine, Mellaril, Miltown, Suavitil, and Librium are presented. Mention is made of the MAOI, Marsalid, Catron and Monase which have been withdrawn from the market. The effectiveness of Tofranil and Elavil are indicated but precaution is emphasized in the danger of giving the iminodibenzyls and MAOI concomitantly.

Univ. of North Carolina, School of Medicine Chapel Hill, N. C.

3 Jacobsen, Erik. The classification of psychotropic drugs. Journal of Neuropsychiatry, 1963, 4, 241-246.

Drugs can be grouped because of 1) similar pharmacological properties, 2) general effects, 3) autonomic effects, 4) effect on EEG arousal, 5) extrapyramidal effects and 6) clinical application. The difficulties in classifying drugs are pointed out by indicating the similarities and dissimilarities of: LSD, mescaline, amphetamine, pipradrol, iproniazid, reserpine, diphenhydramine, benactyzine, hyoscine, atropine, imipramine, amitriptyline, chlorpromazine, promethazine, diethazine, haliperidol, methaminodiazepoxide, carisoprodol, meprobamate, mephenesin, zoxazolamine, phenaglycodol, barbiturate, alcohol, and ether.

Dumex Limited, Copenhagen, Denmark

4 Mason, Aaron S., Forrest, Irene S., Forrest, Fred M., & Butler, Herbert. Adherence to maintenance therapy and rehospitalization. Diseases of the Nervous System, 1963, 24, 103-104.

Forrest and urine color tests indicate that 68 percent of readmission patients had discontinued maintenance medication or placed themselves on a lower dosage. Findings from the urine color tests were correlated with the patient's prescribed medication schedule. High percentage of those readmissions who had adhered to medication emphasize the need for dosage adjustment and attention to psychosocial factors to help the patient meet the environmental stress of community living.

Veterans Administration Hospital, Brockton, Mass.

5 Ayd, Frank J. Five years of antidepressant therapy. M.I.N.D. Psychiatry in General Practice, 1963, 1, 6-11.

Iminodibenzyl derivatives and monoamine oxidase inhibitors represent true advances in treatment of depression. This review covers classification, pharmacological aspects, side effects, and allergic reactions of amine oxidase inhibitors (hydrazine and nonhydrazine) and iminobenzyl derivatives (imipramine, amitriptyline, desipramine, nortriptyline, amimethyline). A major difference between the hydrazine and nonhydrazine enzyme inhibitors appears to be that the slower acting compounds (hydrazines) are more likely to cause side

effects and the nonhydrazines take effect more quickly and cause fewer and less severe side reactions. Inadequate dosage and/or an insufficient period of administration are often causes of treatment failures which are attributed to drug ineffectiveness.

Franklin Square Hospital, Baltimore, Maryland

6 Klein, Donald F., & Fink, Max. Multiple item factors as change measures in psychopharmacology. Psychopharmacologia, 1963, 4, 43-52.

Experiences with multi-item factor rating scales indicate that item analysis may provide a better reflection of behavioral change than status factors. The subjects were patients suffering from acute mental disorders and were seen in individual psychotherapy before the drugs were prescribed. Psychotherapy and intensive milieu therapies continued during the study. Seven rating scales were used to quantify and refine descriptions of behavioral change. Psychiatrists' interview results were coded before medication and after five weeks of treatment. 143 patients received a placebo, 52 patients received imipramine, and 48 received chlorpromazine and procyclidine under double-blind conditions. In an analysis of covariance, the scores of the chlorpromazine treated group showed reduction in manic excitement, melancholy agitation, and motor disturbance. In the covariance analysis by diagnostic subgroup, relative to the placebo, chlorpromazine decreased manic excitement and imipramine increased manic excitement. Global improvement was rated by two psychiatrists. Analysis of change sensitive items was done within the diagnostic subgroups. The pattern of change sensitive variables may be useful in characterizing psychiatric population.

Hillside Hospital, Glen Oaks, L.I. N. Y.

7 Cares, Reuben M., & Buckman, Charles. Comparative review of the structure and side effects of newer psychotropic agents. Diseases of the Nervous System, 1963, 74, 92-105.

23 phenothiazines, 18 nonphenothiazine tranquilizers, and 10 antidepressants are classified by chemical structures and characteristic side effects. This review is based on the 1960-62 literature and the authors' experiences. The "newer psychotropic agents" are those introduced in the last decade which are primarily intended to modify behavior in all forms of mental disorder, excluding the older drugs which affect the central nervous system and the psychotomimetics. Several drugs have been withdrawn from the market because of side effects. They include acepromazine, pheniprazine, iproniazid, cyclopentamine, amphenidone, and etryptamine. Increased use of chemotherapy agents in pediatric psychiatry has aroused interest in their effect on the endocrines, body growth, and mental development. Emphasis is placed on the need for periodic laboratory tests for early detection of toxicity.

Kings Park State Hospital, Kings Park, N. Y.

8 Tobin, Joseph. Psychiatric research design on psychoactive drugs in private community. Diseases of the Nervous System, 1963, 24, 123-126.

Research design for community private practice for investigation of psychoactive drugs, should adapt accepted methods of clinical research to the community as it exists. Influential variables in a private practice setting include: 1) orientation, training, and experience of the physician investigator; 2) careful selection of patients so that drug action is aimed at target symptoms on diagnostic categories; 3) patient safety through small prescriptions, checklists, routine laboratory determination and rapid reporting of toxicity and side effects; 4) judicious use of standard administrative and supervisory procedures; and 5) public relations. The instruments and details of design differ between clinical research and experimental science but not the fundamental principle or purpose of their activity.

Research Systems Assoc., Newark, N. J.

9 Gallant, Donald M. Clinical management of side effects and toxicity in psychopharmacologic therapy. Bulletin of the Tulane University Medical Faculty, 1963, 22, 179-186.

An outline of the clinical management of the nontherapeutic effects of the major antipsychotic, antidepressant and antianxiety compounds make it apparent that the only adequate medical approach for most of the

otentially serious reactions is a preventive
ne. The main complications of the phenothia-
ines are: Granulocytopenia, dermatitis, ab-
ormalities in liver function, and seizures;
he main side effects are extrapyramidal phe-
omena, visual disturbances, sedation, and
rthostatic hypotension. The nonphenothia-
ines such as chlorprothixene and prothipen-
yl cause orthostatic hypotension, sedation,
tropine like side effects and, infrequently,
xtrapyramidal disturbances. The butyrophen-
nes have gross side effects: Extrapyrami-
al disturbances, gastrointestinal complaints
nd hypotension. The side effects of pheno-
hiazines are also associated with the rau-
olfia compounds. The MAO inhibitors are all
otentially capable of producing hepatocel-
ular damage. The non-MAO inhibitors have
he same potential side effects as the pheno-
hiazines but they do not potentiate narcotic
r anesthetic agents. The use of MAO inhibi-
ors combined with an antidepressant is spe-
ifically contraindicated. Side effects of
he major antianxiety compounds (chlordiaze-
oxide and meprobamate) are drowsiness and
taxia. Caution is urged regarding the use
f psychopharmacological agents during preg-
ancy.

ulane University School of Medicine, New
rleans, Louisiana.

CLINICAL STUDIES

10 Bragan, James H. Self-dosage in the psychiatric patient. Psychiatry in General Practice, 1963, 1, 21-25.

Chlordiazepoxide is safe, nontoxic, and nonaddicting in long-term treatment of outpatients suffering from anxiety and anxiety neurosis. The diagnoses of the 47 males and 73 females included anxiety neurosis, depressive reactions, obsessive-compulsive reaction, personality disorder, agitated depression, involutional depressive reaction, and alcoholism. 2/3 of the group were chronically ill; 21 patients had previously received EST and others had been on other chemotherapy agents. After 7-10 days the chlordiazepoxide medication was put on a P.R.N. basis. This flexible therapy has continued for two years with 98 patients evaluated as having good to excellent response. Drowsiness, "tired feeling" or weakness of the legs were the only side effects reported. Psychotherapy or occasional office interviews as well as antidepressants and/or EST were also used during the chlordiazepoxide regimen. Of 12 children suffering from anxiety neurosis, the response to treatment was excellent in 3 cases, good in 8 cases and fair in one case.

Lynn, Mass.

11 Brown, George S. Chlordiazepoxide: An effective adjunct to psychotherapy of the neurotic states. American Journal of Psychiatry, 1963, 119, 774-775.

Chlordiazepoxide as an adjunct to psychotherapy or analysis was effective with neurotic patients. Chlordiazepoxide was administered orally. Dose was variable but averaged 10 mg. t.i.d. Evaluation was by the patient's symptomatic relief, his adjustment to situational stress, and his progress in therapy. The patient's diagnosis included anxiety with hysteria, phobic and depressive reactions, obsessive-compulsive states and mixed anxiety. No side effects were noted. Patient-therapist communication was augmented by alleviation of anxiety and relaxation without oversedation.

Concord, N. H.

12 Leahy, M. R., Rose, J. T., & Plowman, R. A preliminary study of phenoxypropazine in the treatment of depression. American Journal of Psychiatry, 1963, 119, 986-987.

Phenoxypropazine appears effective in treatment of depression. 35 depressed female inpatients of a psychiatric unit in a general hospital received phenoxypropazine, thioridazine and a small dose of barbiturate for four weeks. 17 patients had endogenous depression and 18 were reactive depressives. Ankle edema was the only side effect. 3 cases failed to respond to treatment and 21 made a complete recovery.

St. James's Hospital, Leeds, England.

13 Pöldinger, W. Comparison between imipramine and desipramine in normal subjects and their action in depressive patients. Psychopharmacologia, 1963, 4, 302-307.

The action of desipramine and imipramine in normal subjects gives no really good idea of its essential therapeutic properties. In 7 healthy subjects, both drugs cause fatigue, but with desipramine there were sleep disturbances despite a need for sleep. The latent period was quite different with the two drugs and autonomic effects were observed with imipramine but not with desipramine. Desipramine effects a stronger sedation than imipramine in normal subjects, whereas the reverse is true with animals and patients. Desipramine, in the healthy subjects, shows a rather potent depressor effect and slow onset of action, whereas in patients, the drug has a short latent period and has a certain stimulant effect. Imipramine acts slowly in patients but more quickly in healthy persons. It has scarcely any stimulant action in normal subjects or depressive patients.

Cantonal Psychiatric Clinic,
St. Urban, Lucerne, Switzerland

14 Dierks, M. A comparison of two phenothiazines in the treatment of schizophrenics American Journal of Psychiatry, 1963, 119, 775-776.

rifluoperazine and thioridazine are effective tranquilizers but thioridazine does not roduce extrapyramidal symptoms. 109 female atients from parole and closed wards previously treated with trifluoperazine and benztropine (to control parkinsonism symptoms) ere put on thioridazine alone. Only one atient exhibited any signs of parkinsonism n thioridazine, demonstrating its antipsychotic effectiveness without extrapyramidal timulation.

anvers, Mass.

5 Fennell, George. Psychogenic factors in asomotor rhinorrhoea. British Journal of sychiatry, 1963, 109, 79-80.

ontrolled trial of vasomotor rhinorrhoea patients with chlordiazepoxide and placebo indicate the disorder is not psychosomatic. 45 atients in a double blind study were given a hysical examination, histological examination, blood eosinophil count, and a skin test o rule out evidence of allergy. 20 patients ere given a psychiatric evaluation. Either hlordiazepoxide or a dummy capsule were given t.i.d. for two weeks, and the opposite reatment for another two-week course. 9 patients improved with chlordiazepoxide, 22 ere unimproved, 11 improved with both the ctive and dummy capsule, and 3 improved on he placebo. The investigator questions the mphasis on psychogenic factors in vasomotor hinorrhoea, and he warns against accepting his disorder as being of psychosomatic orin.

he Hospital for Sick Children
ondon, England

6 Mann, Joseph. The initiation of treatent of unmanageable psychotics with intraascular administration of trifluoperazine ombined with chlorpromazine. American Journal of Psychiatry, 1963, 120, 74-76.

ombined intramuscular chlorpromazine and trifluoperazine is rapid and highly effective in difficult to manage psychotic patients. Rapid esponse to the combined medication in 36 male sychotics, shortened hospitalization, eliminated restraining periods, speeded readiness or psychotherapy and oral medication, and essened anxiety in and problems for ward personnel.

Toledo State & Receiving Hospital
Toledo, Ohio

17 Ban, T. A., Ferguson, K., Lehman, H. E. The effect of clopenthixol on chronic psychiatric patients. American Journal of Psychiatry, 1963, 119, 984-985.

Clopenthixol is an effective antipsychotic with low toxicity in some chronic schizophrenics. In this uncontrolled trial with 20 chronic patients consisting of 13 schizophrenics, 2 hypomaniacs, 1 paranoid, 2 mentally deficient psychotics, 1 patient with pathological personality, and 1 chronic alcoholic, clinical observations and a battery of tests indicated improvement in 9 patients, and 11 patients were unchanged or worse. Side effects include paroxysmal tachycardia, dry mouth, skin and scalp, facial flushing, extrapyramidal symptoms, depressive mood change, and drowsiness.

Verdun Protestant Hospital
6875 LaSalle Blvd.
Verdun, Quebec, Canada

18 Lowinger, Paul. Evaluation of mephenoxalone in a single- and double-blind design. American Journal of Psychiatry, 1963, 120, 66-67.

Mephenoxalone appears useful with anxious, psychoneurotic outpatients. 10 female and 16 male anxious patients including schizophrenics, manic depressives, psychoneurotics and personality disorders, given psychiatric and physical examinations, were treated with oral mephenoxalone for 12 to 120 days. Evaluation on a Likert-type scale, physicians progress notes, sleep and/or disturbances, and interpersonal relationships. Pilot single-blind study, 3 of 9 patients improved; double-blind study 30 percent improved with mephenoxalone and 24 percent with the placebo. Side effects included anxiety, insomnia, dizziness, tinnitus, drowsiness, vomiting, skin rash, fatigue, headaches, somnolence, and burning sensation in abdomen.

Department of Psychiatry
Wayne State University
Detroit, Michigan

19 Robinson, J. T., Davies, L. S., Sack, E. L. N. S., & Morrissey, J. D. A controlled trial of abreaction with lysergic acid diethylamide (LSD-25). British Journal of Psychiatry, 1963, 109, 46-53.

Clinical assessment of psychoneurotic inpatients in a controlled trial indicates no significant difference between recovery with standard psychotherapy, and abreaction induced by LSD-25 or Cyclonal/Methedrine. 87 short-term patients who were between 18 and 35 and were of average or above intelligence were treated for 8 weeks by either individual psychotherapy, or by abreactive agents (oral LSD-25 or intravenous hexobarbitone sodium and methylamphetamine). The patients were evaluated on their symptom appraisal and disability at the onset and completion of treatment, and 3 months and 6 months after discharge. Abreactive therapies were no more effective than standard therapy. LSD was more useful in anxious than in passive patient.

Roffey Park Rehabilitation Centre
Horsham, Sussex, England

20 Darling, Harry F. The treatment of ambulatory adolescent schizophrenia with acetophenazine. American Journal of Psychiatry, 1963, 120, 68-69.

Acetophenazine affects relative remission in ambulatory schizophrenic children and adolescents. 72 percent showing "marked" improvement was due in part to their early illness. Lack of parkinsonism outweighs the problem of lethargy.

159 Swan Street
Methuen, Mass.

21 Smith, Marshall E. Perphenazine and amitriptyline as adjuncts to psychotherapy. American Journal of Psychiatry, 1963, 120, 76-77.

Combination of perphenazine and amitriptyline is an effective adjunct to psychotherapy in 65 outpatients with both depression and anxiety. Results are more favorable in depression with and in anxiety reactive, involutional neurotic depression than in alcoholism, conversion reactions or schizophrenia. Dryness of mouth is the major side effect.

Guilford, Connecticut

22 Tutunjian, K. H., & Guido, J. A. A new piperidine phenothiazine (peperacetazine) in chronic, psychotic patients. American Journal of Psychiatry, 1963, 119, 776-777.

Peperacetazine improved the combative, hyperactive behavior of chronic psychotic patients. In 20 backward female patients, 17 were diagnosed as having schizophrenic reactions and 3 had chronic brain syndrome. All were combative and some manifested delusional ideas of persecution, hallucinations, destructive behavior, and intentional incontinence. The group had not responded to other treatments. A maintenance dose of 75 mgm. of peperacetazine per day was determined on a clinical basis for the 4-month trial. Each patient who served as his own control received a complete physical and neurological examination as well as a hemogram, urinalysis, chest x-ray, and liver function tests. The ward milieu was unchanged and the patients' clinical status was evaluated weekly. 50 percent of the group showed marked remission of symptoms after 3-4 days. Treatment lasted 4 months but follow-up evaluations covered 6 months. Status epilepticus, nausea, emesis, and bradycardia were the only side effects and those symptoms disappeared with dosage reduction.

Metropolitan State Hospital
Norwalk, California

3 Rinsley, Donald B. Thioridazine in the reatment of hospitalized adolescents. Ameri-an Journal of Psychiatry, 1963, 120, 73-74.

hioridazine is effective in acute treatment f anxiety and has promoted freer interaction mong adolescent inpatients. Long-term study n a dynamically oriented, intensive treat-ent unit shows thioridazine relatively free f side effects except for mild parkinsonism nd subjective somnolence.

ansas Treatment Center for Children
opeka State Hospital
opeka, Kansas

4 Rickels, K., Snow, L., Baumm, C., & Mock, . Controlled evaluation of several tranquil-zing agents in anxious neurotic outpatients. merican Journal of Psychiatry, 1963, 119, 093-1094.

ead and Johnson 5055 is more effective than mphenidone, I.S. 813 and McN-X-181 in treat-ng anxious, neurotic outpatients. Double-lind crossover method was used in all 4 tri-ls. Each patient served as his own control. of the 4 drugs failed to show significant rug-placebo differences. McN-X-181 produced he most disturbing side effects (dizziness, lurring vision, numbness, mild edema); I.S. 13 and amphenidone produced drowsiness, and ead and Johnson 5055 produced drowsiness nd sedation.

epartment of Psychiatry
niversity of Pennsylvania
hiladelphia, Pennsylvania

5 Garry, J. W., & Leonard, T. J. Trial f amitriptyline in chronic depression. Brit-sh Journal of Psychiatry, 1963, 109, 54-55.

mitriptyline is effective in chronic depres-ives. In this double-blind crossover study, 0 depressed male and female patients with oor response to other drugs and ECT, were ivided into 2 groups for a trial of 2 six-eek periods. The drug and placebo were giv-n each group so that each group formed its wn control. Urinalysis, blood urea, haemo-lobin, liver function tests, and symptom evaluation were carried out before and dur-ing the trial. Side effects included dry mouth, stomatitis, hypotension and dizziness.

St. Audry's Hospital
Melton, Woodbridge, Suffolk, England

26 Rosenberg, D. E., Isbell, Harris, & Miner, E. J. Comparison of a placebo, N-dimethyltryptamine, and 6-hydroxy-N-dimethyl-tryptamine in man. Psychopharmacologia, 1963, 4, 39-42.

DMT produces marked mental effects and autonomic changes in man, whereas 6-HDMT and a placebo do not produce significantly different effects. Five former opiate addict volunteers participated in the single-blind crossover study. Intramuscular DMT, 6-HDMT (in equal doses) and a placebo were given in random order at weekly intervals. Rectal temperature, respiratory rate, pulse rate, blood pressure, pupillary size, kneejerk threshold, and subjective responses were determined. Subjective and autonomic effects of DMT resemble those of LSD. The study suggests that 6-HDMT is not the active metabolite responsible for the effects of DMT.

PHS Hospital
Lexington, Kentucky

27 Kaneko, Ziro, Tanimukai, Hiroshi, Nishinuma, Keiji, & Nishimura, Tsuyoshi. Beta-piperonylisopropylhydrazine a new monoamine oxidase inhibitor as an antidepressant. Psychosomatics, 1963, 4, 99-103.

B-piperonylisopropylhydrazine is effective with depressed patients without serious side effects. Biochemical studies in guinea pigs indicate low toxicity of Safrazine on peripheral tissues and that it inhibits brain MAO more intensely than liver MAO with the chronic administration of a small dose. Clinical studies indicate good results in affective disturbances in depressives. Side effects were transitory dizziness and a fall of blood pressure. Rapid withdrawal of the drug caused a relapse of symptoms, so that a maintenance dose which was reduced gradually was desirable.

Osaka Univ. Medical School, Osaka, Japan

28 Diamond, Seymour. Use of amitriptyline hydrochloride in general practice. Illinois Medical Journal, 1963, 4, 347-348.

Amitriptyline is effective with depressed ambulant patients. 72 patients in a general practice were treated with 25 mg. T.I.D. or q.i.d. or 10 mg. t.i.d. or b.i.d. of amitriptyline hydrochloride for a period not exceeding 3 months. Side effects consisted of dryness of mouth in 10 patients, profuse sweating in 3 and dizziness in 3 patients. 21 of 28 patients with anxiety and simple depression improved; 10 out of 11 reactive depressives improved, 1 schizophrenic improved; 18 out of 22 patients with involution reaction improved; 1 of 3 manic-depressives showed slight improvement.

Chicago Medical School
Chicago, Illinois

29 Dabbs, Alan R., & Paterson, Hugh F. Controlled trial of P2647 in elderly psychiatric patients. British Journal of Psychiatry, 1963, 109, 300-302.

Benzquinamide appears therapeutically effective and without side effects in elderly psychiatric patients. The doubleblind crossover trial with agitated, anxious, uncooperative, elderly patients showed no significant difference between oral doses of 50 mg. of P2647 q.d.s. and 25 mg. of promazine q.d.s. Patients were evaluated on a rating scale concerned with ward behavior and affective state. Blood counts and liver function tests were also carried out. No evidence is presented to indicate that benzquinamide is more effective than promazine hydrochloride in this type of patient.

Oakwood Hospital, Maidstone, England

30 Davison, K. Evaluation of a new tranquilizer--benzquinamide (P2657) by a sequential method. British Journal of Psychiatry, 1963, 109, 539-543.

Benzquinamide is more effective than a placebo, but not amylobarbitone (with the same dose) in anxious outpatients. 15 women and 5 men in good physical health but suffering from anxiety states were given 50 mg. of either P2647, amylobarbitone or lactose 4 times daily for 10 days. At 10-day intervals they were interviewed and assessed their own symptoms. The medication was changed at this time. The patients were also rated on the Hamilton Anxiety Rating Scale and liver function, blood, and urine tests were made. Qualitative comparison of the 3 drugs according to patients' subjective evaluation was made using sequential analysis. Quantitative assessment of the treatment by the anxiety rating scale was done by the sequential T test. There were no toxic effects and the only consistent side effect was transient dizziness.

National Hospital for Nervous Disease
Queen Square, London, W.C.1, England

31 Brooks, G., Weaver, L., Ravaris, C.L., & MacDonald, M. The effect of potassium on phenothiazine-induced extrapyramidal system dysfunction. American Journal of Psychiatry, 1963, 119, 1096-1097.

Supplemental oral potassium did not reduce the incidence or severity of extrapyramidal motor system (EPS) dysfunction in a double-blind study on female patients treated with fluphenazine. 16 schizophrenics and 4 manic-depressives received clinical examinations for EPS dysfunction, psychomotor testing, and fasting serum potassium determinations. These patients were then divided into experimental and control groups. Each group received fluphenazine for the first week, 5 mg. daily; second week, 10 mg. daily and third week, 20 mg. daily. The experimental group was also given 1.25 gms. of potassium in 2 ounces of lemonade t.i.d. and the control group a matching placebo. There was increase in incidence and severity of EPS dysfunction in 7 of 10 in experimental group and 3 of 10 in control group.

College of Medicine
University of Vermont
Burlington, Vermont

32 Hankoff, Leon D., Rudorfer, Leon, & Paley, Herbert M. The antidepressant use of N-(2,5 dimethyl-1-pyrrolyl)-isonicotinamide (SQ 3242). A double blind outpatient evaluation. Journal of New Drugs, 1963, 3, 40-47.

N-(2,5 dimethyl-1-pyrrolyl)-isonicotinamide is effective with ambulatory patients manifesting clinical depression. 68 depressives in a city hospital outpatient clinic particpat

in this double-blind crossover study comparing the hydrazine derivative to a placebo. The dose was 50 mg. 3 times daily. The treatment was assessed by: target symptom rating scale, progress notes of psychiatrist, global change as rated by a psychiatrist, psychiatric rating scale items of depression and apathy, and patient's mood check list. The incidence of clinical attrition and side effects were greater with SQ 3242. Results of the crossover were ambiguous as the therapeutic efficacy of the drug was no longer demonstrable in the second 2 months of the study.

King's County Psychiatric Hospital
Brooklyn, New York

33 Constant, George A., & Gruver, Frank A. Preliminary evaluation of diazepam in psychiatric disorders. Psychosomatics, 1963, 4, 80-84.

Diazepam is effective with anxious, depressed patients and is compatible with antidepressants and ECT. 129 females and 54 males in a hospital setting and private outpatients with a variety of psychiatric disorders were given 6 mg. to 30 mg. daily of diazepam for a mean duration of 8 months. Side effects occurred in 24 patients and included lethargy, rash, drowsiness, ataxia, and hyperactivity. Laboratory studies were obtained periodically. The drug was evaluated on the basis of symptom relief with excellent response in 96 patients, good in 45, fair in 21, and poor in 21.

306 North Moody
Victoria, Texas

34 Barron A., Rudy, L. H., & Smith, J. A. Comparison of a psychoactive drug and an anabolic steroid in chronically ill mental patients. American Journal of Psychiatry, 1963, 119, 1172-1173.

In a double-blind crossover study of 30 chronic female patients, primarily schizophrenic, 10 improved on carphenazine, 3 on oxymetholone, and none on a placebo. Laboratory tests and records of behavioral changes were used in determining results. No serious side effects occurred with carphenazine but an increase in agitation occurred with the placebo and oxymetholone. The dosages given daily, orally, were increased at 10-day intervals.

Illinois State Psychiatric Institute
Chicago, Illinois

35 Lapolla, A. Clinical study of piperazine tranquilizer. Clinical Medicine, 1963, 70, 347-351.

Piperazine, effective in older age patients, was not particularly effective in younger patients and those in the schizophrenic categories. Piperazine was administered over a 4 1/2-month period in total daily dose of 400-800 mg. to mentally ill women averaging 36 years and mentally ill men averaging 64 years. Side effects were drowsiness, slight tremor and rigidity appearing in patients receiving over 400 mg. daily and were relieved by an antiparkinsonian agent.

Camarillo State Hospital
Camarillo, California

36 Abrams, Alfred L. Imipramine in enuresis. American Journal of Psychiatry, 1963, 120, 177-178.

A double-blind study shows imipramine clinically and statistically has no specific effect with enuretic children. 13 children between 8-1/2 and 15 years suffering from personality maladjustment, anxiety, mixed neurosis, or delay and irregular maturation were given imipramine or a placebo. After a month the drugs were reversed so that each patient served as his own control. The children were free of organic disease and safegards against drug reactions were established. 4 children over 12 and 4 under 12 stopped wetting with initial administration of drug or a placebo.

Woodycrest
Bronx, New York

37 Hutchinson, John T., & Smedberg, Daphine. Treatment of depression: A comparative study of ECT and six drugs. British Journal of Psychiatry, 1963, 109, 536-538.

ECT is significantly superior to phenelzine,

imipramine, pheneprazine, amitriptyline, Parstelin, and chlorprothixene in treating depressed female inpatients; imipramine and Parstelin were significantly more effective than amitriptyline, Cavodil, phenelzine and chlorprothixene which were all comparable in action. The seven treatments of 3-week duration were evaluated by means of a blind technique. Four assessments of symptoms were made. ECT appears valuable in dispersing ideas of unworthiness.

Cane Hill Hospital
Coulsdon, Surrey, England

38 Hoffer, A. Nicotinic acid: An adjunct in the treatment of schizophrenia. American Journal of Psychiatry, 1963, 120, 171-173.

Schizophrenic patients treated with nicotinic acid as an adjunct to ECT or tranquilizers have fewer readmissions than non-nicotinized patients. Analysis of readmission data on schizophrenic patients indicate a saving in hospital costs if all patients had received nicotinic acid therapy. Maintenance on nicotinic acid also appears desirable.

Psychiatric Research, Department of Public Health
Saskatoon, Saskatchewan, Canada

39 Pimley, K. G. Thioproperazine: A study of its uses in psychotic excitation. Psychopharmacologia, 1963, 4, 377-384.

Thioproperazine is safe and effective in management and treatment of psychotic excitement. 50 male inpatients with various diagnoses but all having acute excitation were treated with intramuscular (then oral) thioproperazine. Laryngospasm occurred in 3 patients but this was controlled by promethazine-hydrochloride. 43 patients were discharged symptom-free, 6 showed remission of psychotic excitation, and one patient was unimproved. Paradoxical contrast between pharmacological and clinical findings were discussed. i.e., no sedative properties pharmacologically, yet possessing potent sedative activity clinically.

Parkside Hospital, Macclesfield
Cheshire, England

40 Kinross-Wright, John, Vogt, Alfred H., & Charalampous, K. D. A new method of drug therapy. American Journal of Psychiatry, 1963, 119, 779-780.

25 mg. subcutaneous injection of fluphenazine enanthate every 14 days is effective with schizophrenics. In one manic patient and 146 schizophrenics, treated from 2 weeks to 6 months, clinical effects were comparable to fluphenazine. Extrapyramidal side effects occurred in over one-half of the group. Dizziness, insomnia, dryness of mouth and disturbance of visual accommodation were noted. Acute patients responded better than chronic, 17 patients were unimproved, 40 showed relief of some major symptoms, 68 showed relief of many symptoms and 22 achieved remission of their illness. Advantages of slow release preparations, such as fluphenazine enanthate as maintenance medication for outpatients is discussed.

Psychopharmacology Center, Houston
State Psychiatric Institute
Houston, Texas

41 King, John T., Barry, Michael C., & Neary, Edward R. Perinatal findings in women treated during pregnancy with oral fluphenazine. Journal of New Drugs, 1963, 3, 21-25.

In 7 studies involving 394 pregnant women given fluphenazine or a placebo for nausea and vomiting, the incidence of malformations approximates that of the general population. The test group consisted of 244 women and the control group 150. Fluphenazine was given to the large majority during the first gestational trimester. Delivery and neonatal records reveal similarities to expected rates of spontaneous abortion, perinatal mortality, premature birth, and twinning in both groups. Congenital malformation occurred in 2.7 percent of the test group and in 3.5 percent of the control group.

White Laboratories, Inc.
Kenilworth, N. J.

42 Coppen, Alec, Shaw, David Murray, & Farrell, John P. Potentiation of the antidepressive effect of a monoamine-oxidase inhibitor by tryptophan. The Lancet, 1963, 7272, 79-81.

Tranylcypromine in depressive illness is potentiated by tryptophan both during and after the period of administration. In a controlled trial, depressed patients who were treated with tranylcypromine were given tryptophan or a placebo three times a day. Symptoms were assessed by the Hamilton scale. Blood pressure readings, tendon reflex tests, and notes of side effects were made at intervals. Hypotension, drowsiness, feeling of being "drunk," and ataxia occurred with tryptophan. Significant improvement was observed in patients receiving the aminoacid.

Neuropsychiatric Research Unit
Carshalton, and St. Ebba's Hospital
Epsom, Surrey, England

43 Marton, Mary E. A comparative trial of imipramine and phenelzine in the treatment of depression. British Journal of Psychiatry, 1963, 109, 279-285.

Imipramine appears to be a more effective antidepressant than phenelzine in a comparative, single-blind trial of 96 patients. After 4 weeks of therapy, 76 percent of the depressed inpatients and outpatients improved on imipramine and 57 percent on phenelzine although side effects were greater in the imipramine group. All patients received the active drug and corresponding placebo of the other at the same time. Ratings of symptoms and depth of depression, blood pressure, weight, and side-effects were assessed weekly. A 3-month follow-up was done by interview or letter. It is suggested that this method would be of value in rapidly comparing a new drug to another of known value.

St. Patrick's Hospital
Dublin, Ireland

44 Belden, Ernest, & Hitchen, Richard. The identification and treatment of an early deprivation syndrome in alcoholics by means of LSD-25. American Journal of Psychiatry, 1963, 119, 985-986.

LSD is a useful adjunct to therapy with alcoholic patients who evidence an emotional deprivation syndrome. Alcoholic patients in a large mental hospital who had experienced extreme emotional and affectional deprivation at a very early age were treated with LSD therapy and regular psychotherapy. The patients' defenses were often breached by an intensely magnified transference. Treatment was viewed as similar to intensive existentialist "encounter."

Napa State Hospital
Imola, California

45 Abrahams, David. Treatment of encopresis with imipramine. American Journal of Psychiatry, 1963, 119, 891-892.

Imipramine completely alleviated encopresis in a 9-year-old female referred for psychotherapy because of persistent encopresis, masturbation, temper tantrums and indistinct speech. A variety of treatments failed to ameliorate encopresis. She was started on 25 mg. daily of imipramine, which had been encouraging in enuresis, and the encopresis ceased on the following day. Imipramine was administered daily for more than one month without any side effects. Encopresis returned when a placebo was substituted. The child's milieu improved and she appeared happier and calmer and had better control in frustrating situations. She was continued on imipramine 25 mg. daily for over two months along with weekly supportive psychotherapy. On the basis of this report further clinical trials are indicated.

Harbor General Hospital, Torrance, Calif.

46 Singh, Harbhajan. Therapeutic use of thioridazine in premature ejaculation. American Journal of Psychiatry, 1963, 119, 891.

Thioridazine was used successfully in a case of premature ejaculation. Thioridazine's property of delaying ejaculation was proved valuable in treating a neurotic patient who was anxious and sexually insecure because of premature ejaculation. He was placed on 25 mg. of thioridazine t.i.d. and 25 mg. t.i.d. of imipramine.

1105 Carling Avenue
Ottawa 3, Canada

47 Hollister, Leo E., Bennett, J. L., Kaim, Samuel C., & Kimball, Isham, Jr. Drug-induced EEG abnormalities as predictors of clinical response to thiopropazate and haloperidol. American Journal of Psychiatry, 1963, 119, 887-888.

No relationship was shown between EEG abnormalities from tranquilizing drugs and clinical response of individual patients. EEG and clinical evaluations (on Brief Psychiatric Rating Scale) were obtained on 40 patients before treatment and after 6 weeks in a controlled comparative study of thiopropazate and haloperidol. Inpatients showed definite change from normal to abnormal tracings, 14 patients had normal tracings on both occasions and the remainder either equivocal changes from initially normal tracings or equivocal or definitely abnormal initial tracings. All drug-induced abnormalities consisted of mild slowing of rhythm. The mean induction of pathology in the group which showed persistently normal tracings was 23.1 and for those showing drug-induced synchronization, it was 19.0.

V.A. Hospital, Palo Alto, Calif.
V.A. Cooperative Studies of Chemotherapy in Psychiatry

48 Gallant, D. M., Bishop, M. P., Steele, C. A., & Noblin, D. D. The relationship between serotonin antagonism and tranquilizing activity. American Journal of Psychiatry, 1963, 119, 882.

The therapeutic effects of a placebo and methysergide with chronic schizophrenics did not differ. 40 male and female subjects were divided into 3 groups and given 800 mg. daily of chlorpromazine, 16 mg. daily of methysergide or a placebo. The double-blind study lasted 12 weeks. Evaluation of drug effects included the Lorr Psychiatric Rating Scale, global ratings of improvement, the Tulane Research Battery of psychological tests, and routine laboratory measures. The rating measures did not demonstrate differences in therapeutic effect between UML-491 and the placebo, but chlorpromazine did produce definite beneficial effect with 56 percent showing significant clinical improvement.

Tulane University School of Medicine
New Orleans, La.

49 Spencer, A. M. Permissive group therapy with lysergic acid diethylamide. British Journal of Psychiatry, 1963, 109, 37-45.

Patients with a poor prognosis responded well to LSD in a group abreacted setting. 10 chronic female patients (half inpatients and half outpatients) who suffered from psychopathy, hysteria, phobic anxiety, or recurrent neurotic depression were treated for 16 months with a combination of LSD and group therapy twice a week. The staff members were a doctor and nurse, acting as parent surrogate The treatment room was furnished like a Child Guidance Play Therapy Room, with tailor's dummies serving as bad parent surrogates. Physical effects of LSD appeared the same as in individual treatment. The chief etiological factor in the neurotic illness of the patients seemed to be rejection by parents, especially the father, during early childhood. Thus treatment objective was to bring into consciousness their repressed feelings of rejection and to find in the acceptance of themselves by the new father, mother, and sib surrogates a basic security, enabling the to direct feelings constructively outward rather than destructively inward. Permissiveness and the physical contiguity allowed between patients and therapists were of great value to many patients. In most cases positive transference developed with ease. 3 patients improved so as to no longer require psychiatric help, 4 were helped to a fairly definite degree, and 3 patients remained unimproved.

Powick Hospital, Nr. Worchester, Great Britai

50 Tuteur, Werner. Tranquilizers and psychosomatic illness. American Journal of Psychiatry, 1963, 119, 787-788.

Cases of psychosomatic illness were relieved by chlorpromazine. 2 cases of globus hystericus and 1 of cardiovascular neurosis were quickly relieved by 75 mg. chlorpromazine spansules. Discontinuation of medication caused reoccurrence of symptoms but reinstitution of the drug brought prompt relief. N side effects were reported.

Elgin State Hospital
Elgin, Illinois

51 Cheng, Sylvia F., & Fogel, Ernest J. Trifluoperazine combined with amitriptyline in paranoid psychosis. American Journal of Psychiatry, 1963, 119, 780-781.

Females with acute schizophrenia or paranoid psychosis improved on trifluoperazine-amitriptyline with few side effects. 100 schizophrenics with paranoid features were given 5 to 10 mg. of trifluoperazine b.i.d. or t.i.d. with 25 mg. (or occasionally 50 mg.) of amitriptyline t.i.d. and chlorpromazine, thioridazine, chlorprothixene, or chlordiazepoxide to control motor disturbances. 95 improved. The usual extrapyramidal side effects of trifluoperazine were minimized by amitriptyline. The drug combination was equally successful with 25 patients suffering from paranoid psychosis associated with mental disorders other than schizophrenia.

Logansport State Hospital
Logansport, Indiana

52 Halas, Evan J. Further data to the clinical effects of nialamide. American Journal of Psychiatry, 1963, 119, 785-786.

After unsuccessful treatment with other antidepressants, 300 mg. of nialamide was instituted in a chronically depressed patient with colitis and eczema. There were changes in the patient's appetite, sleep pattern, water metabolism, and carbohydrate metabolism and the eczema and colitis disappeared. Between the 7th and 8th week of treatment, preceded by evidence of fluid retention, an episode of rise in blood pressure, decreased pulse rate and excruciating headache occurred. Reduction in dosage did not prevent 2 further attacks and therapy was discontinued. The eczema and colitis then reappeared. The effects on sleep, behavior, appetite and water metabolism are considered evidence for a diencephalic site of action for nialamide.

Columbus State Hospital
Columbus, Ohio

53 Pöldinger, W. Combined administration of desipramine and reserpine or tetrabenazine in depressive patients. Psychopharmacologia, 1963, 4, 308-310.

Depressed patients who were unresponsive to desipramine were made responsive by injections of reserpine or tetrabenazine. 7 of 11 imipramine-resistant patients responded favorably after 7-10 mg. of reserpine i.m. for 1 or 2 days. In 7 desipramine-resistant patients, 2,5-7,5 mg. of reserpine or 50-100 mg. of tetrabenazine i.v. or i.m. were administered. 4 patients showed a distinct excitation state with autonomic side effects followed by improvement of the depressive mood. In the other 3 patients no distinct response was manifested. This study is reminiscent of animal experiments in which the typical reserpine syndrome can be antagonized by pretreatment with imipramine or desipramine.

Cantonal Psychiatric Clinic
St. Urban, Canton of Lucerne
Lucerne, Switzerland

54 Ideström, Carl-Magnus, & Cadenius, Björn. Chlordiazepoxide, dipiperon and amobarbital. Dose effect studies on human beings. Psychopharmacologia, 1963, 4, 235-246.

Chlordiazepoxide and dipiperon have an inhibiting effect on some central nervous functions while they affect only slightly other functions, primarily psychomotor. Effect of chlordiazepoxide, amobarbital and dipiperon on 21 healthy male student volunteers were studied with the double-blind technique and the following experimental-psychological tests: choice reaction time, tapping speed, flicker fusion, hand coordination, standing steadiness, and counting and discriminating tones. A subjective questionnaire on tiredness, sleepiness and similar side effects was also completed. Results indicate: 1) CFF is reduced by 20 and 40 mg. of dipiperon; 20 mg. chlordiazepoxide cause no significant impairment, but 40 mg. do, 2) psychomotor functions are impaired more by chlordiazepoxide than by dipiperon, 3) 150 mg. of amobarbital produce significant impairment of CFF and tapping speed whereas 300 mg. of amobarbital elicit significant improvement, 4) 450 mg. of amobarbital cause marked impairment of all functions tested.

Karolinska Sjukhust
Stockholm 60, Sweden

55 Singer, K. Gilles de la Tourette's disease. American Journal of Psychiatry, 1963, 120, 80-81.

Gilles de la Tourette's disease was successfully treated with combined chlordiazepoxide and isocarboxazid. A 15-year-old Chinese boy developed multiple tics, anxiety, obsessional phenomena, and coprolalia. Blood count, chest and skull x-rays and EEG were normal. Psychological testing showed dull normal range. Treatment consisted of reduction of environmental stresses and psychotherapy. Chlorpromazine, trifluoperazine and amphetamine were unsuccessful. 30 mg. of chlordiazepoxide and 20 mg. of isocarboxazid daily were instituted and considerable improvement was noticed within one week.

Government of Hong Kong
Castle Peak Hospital, Hong Kong
Hong Kong, China

56 Nussbaum, Kurt, & Kurland, Albert A. Intravenous administration of Indoklon 10 percent solution. American Journal of Psychiatry, 1963, 120, 69-70.

10 percent solution of Indoklon administered intravenously brought about symptomatic improvement in psychotic patients. 14 schizoaffective or depressive patients were administered Indoklon preceded by intravenous succinylcholine chloride. Atropine sulfate was given intramuscularly half hour prior to treatment. Number of treatments varied from 2 to 11 per patient, and ECT was alternated with Indoklon 10 percent in some cases with no observable ill effects. No patient complained of pain radiating up the arm and sclerosis of the veins was not observed with the 10 percent solution as is usual with the 5 percent solution.

Spring Grove State Hospital
Baltimore, Maryland

57 McQuillen, Michael P., Gross, Martin, & Johns, Richard J. Chlorpromazine-induced weakness in myasthenia gravis. Archives of Neurology, 1963, 8, 286-290.

Weakness in a paranoid myasthenic schizophrenic patient was exacerbated by chlorpromazine. Basal studies on the case presented showed a typical myasthenic neuromuscular transmission defect. Studies of muscle action potentials in response to paired and repeated stimuli indicated that chlorpromazine increased the relative degree of block following the passage of a single impulse. Neostigmine corrected the myasthenic block in the presence of chlorpromazine but neostigmine failed to restore the single action potential even to the basal level. Indications are that the weakness is partially due to the neuromuscular blocking effect of the drug and partially to a drug-induced increas in the myasthenic block.

Johns Hopkins University School of Medicine
Baltimore, Maryland

58 Moore, Leroy E. Fluphenazine in the treatment of hospitalized mental patients. American Journal of Psychiatry, 1963, 119, 987-988.

Fluphenazine is effective in the treatment of functional psychiatric disorders. 97 chronic, psychotic male patients and 77 acut schizophrenics were treated with fluphenazi in doses of 1 to 40 mg. orally, parenterally, or as an elixer for periods up to 8 months. Effects of treatment were based on an evaluation of the patient's psychiatric status and weekly reports on the patient's behavior by nurses and attendants. 30 of the 97 chronic patients improved in the first week and an increasing proportion improved as treatment continued. After perio up to 7 months, 47 of the 77 acute patients were improved, 5 were placed on leave, 4 were transferred, and 1 was discharged. 17 patients in the entire series experienced side effects which included: parkinsonlike symptoms, nervousness, insomnia, gastrointe tinal symptoms, vomiting, and drowsiness.

Camarillo State Hospital
Camarillo, California

59 Oltman, Jane E.& Friedman, Samuel. Ev ation of nortriptyline in the treatment of fective disorders (and comparison with ot drugs). American Journal of Psychiatry, 1 119, 988-989.

Nortriptyline is an effective antidepressa in acute or recurrent depressive illness.

epressed female patients received 25 mg. of ortriptyline t.i.d. or q.i.d. initially and 0 mg. t.i.d. after 7 to 10 days. 80 percent f the patients achieved full remission or ere much improved. Improvement usually be- an within 7 to 10 days. Side effects were requent but not distressing. They included: ryness of the mouth, peculiar taste, dizzi- ess, somnolence, weakness, constipation, weating, feeling of warmth, mild manic phase. ll except dryness of the mouth disappeared fter the first week. Laboratory data were ormal. Results of treatment with nortrip- yline compare favorably with imipramine, mitriptyline, and desmethylimipramine.

airfield State Hospital
ewtown, Conn.

0 Maggs, Ronald. Treatment of manic ill- ess with lithium carbonate. British Jour- al of Psychiatry, 1963, 109, 56-65.

ithium carbonate is found to be valuable dur- ng acute manic illness. 18 patients with a- ute manic illness and satisfactory biochemi- al test results completed this double-blind rial of two 14-day periods. 0.5 g., three imes a day of lithium six days a week with day of rest or corresponding placebo was iven each group. Regular clinical appraisal y means of the Wittenborn Psychiatric Rating cale, and blood electrolyte assessment were ade. Blood lithium levels had no relation- hip to therapeutic effect of the drug. One atient was withdrawn from the trial because f drowsiness, ataxia, and tremor of the limbs, nd another because of symptoms of encephalo- athy. The degree of mania diminished signif- icantly during the second week of treatment ith lithium compared with the placebo.

ellingly Hospital, Hailsham
ussex, England

61 Rickels, Karl, & Bass, Harry. A com- arative controlled clinical trial of seven ypnotic agents in medical and psychiatric npatients. American Journal of the Medical ciences, 1963, 245, 142-152.

cutely ill schizophrenic and depressed pa- ients represent a poor population for pre- icting the efficacy of new hypnotic agents n normal patients. 36 medical ward patients took all 7 drugs and placebo and the 20 psychiatric ward patients took 5 drugs and placebo in random order during a 3-month period. A double-blind design was employed and a physician performed ratings of depression, anxiety, irritability, and intensity of somatic pain. In medical patients data show that the higher the psychopathology score, the poorer the response to hypnotic medication. No significant difference between the drugs and placebo were found in the psychiatric patients. In the medical patients using secobarbital sodium 200 mg. as a standard hypnotic, methyprylon 300 mg. produced the most similar results as a hypnotic agent, followed by meprobamate 800 mg., glutethimide 500 mg., and secobarbital sodium 100 mg. The weakest drugs were ethinamate 500 mg. and chloral hydrate 1000 mg.

University of Pennsylvania
University Park, Pa.

62 Vestre, Norris D., MacNaughton, David V., & Schiele, Burtrum C. A comparison of the slow-release and the regular forms of thioridazine: A double-blind controlled study in hospitalized psychiatric patients. Current Therapeutic Research, 1963, 5, 183-194.

Slow release tablets of thioridazine appear to have no advantage over regular tablets with chronic hospitalized patients, whereas the slow release form has slight advantages as medication for patients released from a hospital or especially sensitive to side effects. 58 male veterans (55 schizophrenics, 2 neurotics and 1 patient with chronic brain syndrome) completed the double-blind comparison. They were divided into two groups. Group A received the regular form of thioridazine and Group B the slow-release form. The majority of patients were stabilized on 600 mg. daily. Patient response to treatment was measured by a Behavior and Symptom Rating Scale, Minnesota Follow-Up Study Rehabilitation Rating Scale, Clyde Mood Scale, and a detailed side effects check list. In ratings of ward behavior and symptoms, the 2 forms of thioridazine were essentially identical in effectiveness. The slow-release form had slight advantage with respect to side effects in that cases of blurred vision and muscle weakness were less frequent. Ratings of work performance in physical medicine and rehabilitation activities indicate significant advantages for the

slow-release form. The interrelationship observed suggests a greater facility in manipulation functions in patients on slow-release tablets.

Veterans Administration Hospital
St. Cloud, Minnesota

63 MacLeod, E. C., & Moffat, J. "Continuous" thioproperazine. A controlled trial in chronic schizophrenia. British Journal of Psychiatry, 1963, 109, 531-535.

Results of this study indicate that thioproperazine used in the "continuous" manner is not a particularly suitable or effective treatment in chronic schizophrenia. The double-blind investigation was carried out in four stages: Stage I - No treatment for 1 month; Stage II - Group A received benzhexol (10 mg.) for 3 weeks while Group B received placebo; Stage III - Group A received benzhexol and thioperazine and Group B received equivalent placebos. Stage IV - All treatments discontinued for 2 weeks. Assessment by means of a behavior rating scale were made during the last week of each stage. Patients on benzhexol alone developed no noticeable side effects, but on both active drugs: one developed venous thrombosis, one developed a carbuncle, seven showed anorexia, several appeared pale and unwell, and 4 patients developed extrapyramidal disturbances. The behavior rating scale and clinical assessment showed little or no improvement. Trihexypenidyl appeared to be effective in controlling the extrapyramidal side effects of thioproperazine.

Dept. Psychological Medicine, Southern Gen. Hospital, Glasgow, Scotland

64 Schiele, Burtrum C., Vestre, Norris D., & MacNaughton, David V. Treatment of hospitalized schizophrenics with trifluoperazine plus tranylcypromine: A double-blind controlled study. Comprehensive Psychiatry, 1963, 4, 66-79.

Tranylcypromine does not contribute much to the improvement shown by depressed or withdrawn schizophrenics treated with trifluoperazine alone. 50 schizophrenics with symptoms of depression, anergia or withdrawal were divided into 2 groups. One group was fed trifluoperazine plus tranylcypromine, the other fed trifluoperazine plus placebo. The Psychot Reaction Profile, the Minnesota Multiphasic Personality Inventory and a Symptom Rating Schedule were used for evaluation. Doses were increased daily to the maximum tolerated. In comparing the 2 groups there was no significant difference between them in the above tests. Side effects were controlled by reducing dosage or administering an antiparkinsonian drug. Patients in both groups showed gradual and in some cases marked improvement.

University of Minnesota Hospitals
Minneapolis 14, Minnesota

65 Chang, S. C. Treatment of agitated patients with chlorprothixene. American Journal of Psychiatry, 1963, 120, 71-72.

Schizophrenics with readily identifiable affect respond to low doses of chlorprothixene. 22 male subacute schizophrenics and 4 patients with arteriosclerotic organic brain damage were treated from 1-2 months with 25-50 mg. of chlorprothixene t.i.d. Patients were selected because of agitation and/or refractoriness to neuroleptic or convulsive treatments. 10 patients improved. The unimproved patients were those who show blocking or restraint and their motor function and thought and disorganization of affect-thought pattern. No significant side reactions were noted in hemograms or urograms but there was an occasional hypotensive reaction.

Connecticut Valley Hospital
Middleton, Connecticut

Pogge, Raymond C., & Coats, Edwin A. The
acebo as a source of side effects: Influ-
e of gradually increasing doses. Psychia-
in General Practice, 1963, 1, 61-63.

idence and nature of side effects produced
placebo tended to vary with dosage levels.
49 paid subjects were instructed to take
tablet b.i.d. The first day up to five
i.d. on the fifth day. A simple report
m was provided to record their reactions.
subjects reported no subjective response,
reported various responses associated with
e type of central depression, 8 subjects
orted gastrointestinal discomfort; and 3
jects reported symptoms of central stimu-
ion.

sey Labs., Lincoln, Nebraska

Walters, G. M., Terrence, C., & Steckel,
Jaundice following administration of flu-
nazine dihydrochloride. American Journal
Psychiatry, 1963, 120, 81-82.

acute schizophrenic female treated with
l Prolixin developed mild jaundice, skin
ions, and edema. Physical and laboratory
ts given the patient prior to drug admin-
ration were negative. Drug was stopped
er clinical evidence of toxic reaction.

hester State Hospital, Rochester, N. Y.

Kane, Francis J., Jr., & Freeman, Donald.
fatal reaction to imipramine-MAO inhibitor
bination. American Journal of Psychiatry,
3, 120, 79-80.

fatal reaction to imipramine-etryptamine
bination suggests cautious use of subthera-
tic doses of these agents. A depressed fe-
le with somatic delusions, treated with
all doses of imipramine and an MAO inhib-
r, reacted by a flushed face, difficulty
breathing, and weakness with motor hyper-
tivity. The patient had received imipra-
ne 25 mg. daily for several weeks previ-
, and was then given one 15 mg. tablet of
yptamine which precipitated her reaction.

lversity of North Carolina
pel Hill, North Carolina

69 Vilkin, Morris I. Extrapyramidal side effects of trifluoperazine. Journal of Neuropsychiatry, 1963, 4, 236-239.

As the use of phenothiazines increases, trifluoperazine takes on new importance with its high potency and high incidence of side effects. Two illustrative cases are presented with severe side effects, treatment and course in hospital. The first case was a woman with an acute schizo-affective disorder. She was treated with trifluoperazine and developed severe extrapyramidal symptoms. The trifluoperazine was discontinued and prochlorperazine was discontinued and prochlorperazine was instituted. This was later changed to chlorpromazine. The second case was a female whose symptoms consisted of confusion, bizarre ideation, and delusions. She was treated with trifluoperazine (5 mg.) and chlorpromazine (75 mg.) and became exceedingly drowsy, with severe dysphagia and dysarthria. Trifluoperazine was discontinued and she remained on chlorpromazine and Cogentin. Her extrapyramidal symptoms cleared rapidly. Difficulty in focusing for close vision appears to be a complaint from patients treated with trifluoperazine, even when dry mouth and nasal congestion are not present.

666 East Regent Street
Inglewood, California

70 Kane, Francis J., Jr. Oral moniliasis following the use of Thorazine. American Journal of Psychiatry, 1963, 120, 187-188.

Two cases of oral moniliasis following the use of chlorpromazine, are reported. The first case was that of a male admission to a psychiatric inpatient service following increasing psychomotor activity and aggressive behavior. He was given an oral suspension of chlorpromazine which was increased to 200 mg. q.i.d. In twelve days he developed moniliasis. Mycostatin was given with good remission of symptoms. The second case was an acutely manic female who was heavily sedated with chlorpromazine. She developed an acute dystonic reaction and oral moniliasis. She was placed on Mycostatin and experienced no further symptoms. Further therapy with thioridazine and methanesulfonate was uneventful.

Dept. of Psychiatry, Univ. of North Carolina
Chapel Hill, N. C.

71 Jarecki, Henry G. Combined amitriptyline and phenelzine poisoning. American Journal of Psychiatry, 1963, 120, 189.

Clinical findings in a patient attempting suicide with amitriptyline and phenelzine resemble imipramine-phenelzine poisoning. Impaired consciousness, cardiovascular instability, hyperpyrexia and urinary retention are problems in combined amitriptyline and phenelzine poisoning.

Grace-New Haven Community Hospital
New Haven, Conn.

72 Waldman, Samuel. Unusual manifestations associated with a phenothiazine-induced dystonic reaction. Psychosomatics, 1963, 4, 173-174.

Prochlorperazine induced opisthotonic dystonia in a 16-year-old girl. In the case presented the girl's primary disease was infectious mononucleosis associated with hepatic involvement. Prochlorperazine rectal suppositories were prescribed to control vomiting, and a total of four suppositories (100 mg.) had been used over a two-day period. Urine retention delayed excretion of the drug. In addition to the dystonic reaction and retention of urine, extremely shallow respiratory excursions and dyspnea were evident. The hepatic dysfunction was attributed to the mononucleosis.

Unity Hospital, Brooklyn, N. Y.

73 Isaacs, Anthony D., & Carlish, S. Peripheral neuropathy after amitryptyline. British Medical Journal, 1963, 5343, 1739.

A case of toxic peripheral neuropathy occurred in a depressed patient receiving amitriptyline. A 69-year-old depressed widow received 25 mg. t.i.d. to 50 mg. t.i.d. for depression and agitation. Other than a barbiturate given at night as a sedative, no other medication was administered to the patient. In 15 days she complained of numbness of feet and unsteady gait, and 2 days later marked weakness of dorsiflexion developed. Symptoms subsided when drug was withdrawn.

Cane Hill Hospital
Coulsdon, Surrey, England

74 Bishop, M. P., & Gallant, D. M. Behavioral toxicity associated with benzquinamide (Quantril) therapy in schizophrenic patients. American Journal of Psychiatry, 1963, 120, 180-181.

In a double-blind trial comparing chlorpromazine, placebo, and benzquinamide, only one patient receiving benzquinamide improved and 3 developed severe behavioral toxicity. 3 groups of 10 chronic schizophrenic men and women were studied for 10 weeks. Drug efficacy was measured by the Lorr Psychiatric Rating Scale, Over-all and Gorham Brief Psychiatric Rating Scale, independent global rating, Tulane Research Battery of psychological tests, and routine laboratory measures. 8 of 10 patients improved on chlorpromazine, none on the placebo. The behavioral side effects of benzquinamide were characterized primarily by extreme agitation with general exacerbation of psychotic symptoms, increased depressive ideation, and emergence or intensification of self-destructive behavior. These suggest extreme caution if benzquinamide is used with depressed suicidal, or self-multilative patients.

Dept. of Neurology and Psychiatry
Tulane University, School of Medicine
New Orleans, La.

75 Kane, Francis J., Jr., & Taylor, T. W. An unusual reaction to combined imipramine-Thorazine therapy. American Journal of Psychiatry, 1963, 120, 186-187.

An apathetic patient, treated with 75 mg. of chlorpromazine and 75 mg. of imipramine daily developed impairment of speech, generalized tremor, hyperactive DTR's, persistent clonus, and equivocal Babinski's reflexes. A similar case with movement disorder and impairment of speech in clear consciousness has been reported. Clearing of signs followed supportive care without drugs, although the patient remained tense with weak affect expression and apparent poverty of thought. The unusual syndrome produced by imipramine-chlorpromazine suggests caution in the combined

use of these drugs.

University of North Carolina
Chapel Hill, N. C.

76 Destounis, Nicholas. Thioridazine and amenorrhea. American Journal of Psychiatry, 1963, 120, 188.

A 35-year-old female with an acute schizophrenic reaction of a paranoid type developed amenorrhea during thioridazine therapy. Discontinuation of the drug resulted in a regular period for the patient.

8358 Ohio River Blvd., Elmsworth
Pittsburgh, Pa.

77 Robie, Theodore R. Controlling monoamine oxidase inhibitor hypotension with 9-alpha-fluoro-hydrocortisone. American Journal of Psychiatry, 1963, 120, 170-171.

Miniscle dosage (0.1 mg. daily) of 9-alpha-fluoro-hydrocortisone overcomes and prevents development of MAOI-induced hypotension. This antihypotension agent was successful in 21 patients, taking MAOI therapy, stabilizing ambulant blood pressure. However, because this is a powerful drug, dosage must be reduced as soon as blood pressure is raised to stabilized levels. One case is reported of a 50-year-old undernourished woman who experienced nocturnal hyperkinesia while taking MAOI therapy and required mysoline.

Montclair, N. J.

78 Wilson, Ian C., Gambill, John M., & Sandifer, Myron G. Loeffler's syndrome occurring during imipramine therapy. American Journal of Psychiatry, 1963, 119, 892-893.

A case of extreme eosinophilia with pulmonary infiltration occurred during imipramine therapy. A female patient, 43 years old, with a diagnosis of manic-depressive reaction, depressive type, was admitted to a unit where a double-blind study with imipramine and desmethylimipramine was being undertaken. A therapeutic dose of 50 mg. q.i.d. imipramine was initiated and later was increased to 100 mg. t.i.d. The patient complained of dyspnea on exertion and mechanical respiratory difficulties. Clinical finding appears to be a mild case of bronchial asthma. Clinical findings and a record of her laboratory findings are presented. Imipramine therapy was discontinued. This was interpreted as a case of Loeffler's syndrome occurring as an allergic response to imipramine.

North Carolina Hospitals

79 James, Pierce. Drug-withdrawal psychoses. American Journal of Psychiatry, 1963, 119, 880-881.

Cases of acute withdrawal psychoses, indistinguishable from delirium tremens, followed withdrawal of chloral hydrate, carbromal and sodium pentobarbital. 3 female patients addicted to a hypnotic drug developed drug-withdrawal psychoses clinically resembling the delirium tremens of alcoholism two to three days after admission to a general hospital. In each instance alcohol consumption was discounted. The author suggests that the syndrome of delirium tremens results from the association of a confusional psychosis with the alcohol or sedative drug-withdrawal syndrome, and that the tremulous withdrawal psychosis of sedative drug addiction and the delirium tremens of alcoholism are clinically identical.

Royal Perth Hospital
Perth, Western Australia

80 Rasmussen, E. Boje, & Kristjansen, P. ECG changes during amitriptyline treatment. American Journal of Psychiatry, 1963, 119, 781-782.

Evidence of cardiac complications under amitriptyline is reported. 33 male and 32 female patients with mean age of 60 years were given amitriptyline perorally in dosages varying from 75 to 225 mg. daily for 3 weeks. ECG results were compared to ECG results from periods without administration of psycholeptic drugs. In the male group, evident ECG changes were found in 3 patients, less certain changes in 13, and no change in 17. In the female group, evident changes in 9, less certain in 8, and no change in 15. Changes were T and ST abnormalities and various arrythmias. 3 patients with cardiac disease

deteriorated during amitriptyline treatment. Cautious dosage in elderly patients is considered advisable.

Sct. Hans Mental Hospital
Roskilde, Denmark

81 Kruse, Walter. Development of parkinsonism after gradual reduction of fluphenazine dosage. American Journal of Psychiatry, 1963, 119, 995-996.

Parkinsonism did not develop in 3 patients until several months of fluphenazine treatment and dosage had been reduced. In one case of a deluded and hallucinated male with little expression of affect and two paranoid schizophrenics, a parkinsonian reaction developed after dosage had been gradually decreased from 20-45 mg. daily to 2-5 mg. over several weeks. The extrapyramidal signs disappeared after further reduction of dosage or termination of treatment.

Landeskrankenhaus, Wehnen Post
Ofen, West Germany

82 Prange, Arthur J., Jr. Paroxysmal auricular tachycardia apparently resulting from combined thyroid-imipramine treatment. American Journal of Psychiatry, 1963, 119, 994-995.

Auricular tachycardia occurred during combined thyroid-imipramine therapy. A 65-year-old hypothyroid female was being treated with 6- mg. of thyroid per day. She became depressed and threatened suicide and was treated with imipramine 75 mg. daily. The dose was increased to 150 mg. daily and after 11 days EKG revealed auricular tachycardia. Thyroid medication was stopped and the patient has experienced no cardiac irregularity since that time. Results of animal investigations show imipramine LD_{50} for hyperthyroid mice is 44 percent of the LD_{50} for euthyroid mice and hypothyroid mice are more resistant to imipramine death than euthyroid mice. It is known that in the cat imipramine potentiates the effect of thyroxin on heart rate. Animal studies suggest that the toxicity of both imipramine and MAO inhibitors may be increased in states of hyperthyroidism.

School of Medicine, University of
North Carolina
Chapel Hill, North Carolina

83 Essig, Carl F. Addictive and possible toxic properties of glutethimide. American Journal of Psychiatry, 1963, 119, 993.

Convulsions were observed in dogs after abrupt withdrawal of glutethimide following chronic intoxication. 10 dogs were given 51 to 83 mg./kg. of glutethimide, one daily for 3 and one-half weeks, and doses of 114 to 424 mg./kg. for periods ranging from 113 to 168 days. During chronic intoxication period, the dogs were somnolent and ataxic. 5 died at doses from 300 to 424 mg./kg. day. 1 dog developed 4 major convulsions during abstinence. The need for controlled chronic toxicity studies of glutethimide are indicated.

NIMH Addiction Research Center
PHS Hospital, Lexington, Ky.

84 Harthorne, J. Warren, Marcus, Anthony M., & Kaye, Michael. Mangement of massive imipramine overdosage with mannitol and artificial dialysis. New England Journal of Medicine, 1963, 268, 33-36.

A suicide attempt with 5375 mg. of imipramine was treated in part with artificial dialysis and i.v. administration of mannitol and recovered. A 21-year-old female, addicted to barbiturates and morphine, ingested 215-25-mg. tablets of imipramine. She suffered severe hypotension, convulsive seizures, apnea, cardiac arrest, severe oliguria and hyperpyrexia. Treatment included gastric lavage, vasopressor agents, barbiturates to control seizures and assist respiration. Dialysis controlled the hyperpyrexia but did not remove significant amounts of imipramine. Mannitol was an effective osmotic diuretic.

Department of Medicine
Montreal General Hospital
Montreal, Canada

85 McCormick, T. C., Jr., & McNeel, Tynus W. Acute psychosis and Ritalin abuse. Texas State Journal of Medicine, 1963, 59, 99-100.

A male alcoholic experienced acute psychosis through parenteral self-medication of methylphenidate hydrochloride solution. The patient was prescribed methylphenadate in dosages of 40 to 60 mg. a day by a physician for his alcoholism and later began abusing the drug by taking 100 to 200 mg. a day parenterally. He was admitted to a hospital hyperactive, confused, fearful, and with paranoid delusions. A withdrawal regimen was initiated and included sedatives, anticonvulsants, chlorpromazine, and adequate fluid and nutritional supplements. The question of methylphenadate addiction is raised and prescription for parenteral self-administration is cautioned against.

University of Texas Medical Branch
Galveston, Texas

86 Fisher, Seymour, & Fisher, Rhonda L. Placebo response and acquiescence. Psychopharmacologia, 1963, 4, 298-301

In this sample of college students, placebo response and acquiescence were significantly related. The subjects, who had a median age of 20 years, consisted of 39 women and 33 men. The degree to which the subject identified with a dependent, passive attitude was measured by means of the Bass Social Acquiescence Scale. A polygraph was attached to the subject to enhance the dramatic quality of the situation, but it did not record. The subject was asked to swallow an inert capsule and report its effect. The symptom reports were recorded. At the end of 15 minutes the subject was asked to complete a checklist containing 14 items of "drug reactions" relating to skin, heart, stomach and muscle. Chi-square was used to examine the relationship between the checklist and spontaneous symptom scores. They proved to be linked in a significant fashion. No significant sex differences were apparent for either the spontaneous symptom or checklist scores.

State University of New York
Upstate Medical Center
Syracuse, New York

87 Weissman, Albert. Correlation between baseline nondiscriminated avoidance behavior in rats and amphetamine-induced stimulation. Psychopharmacologia, 1963, 4, 294-297.

Response rates induced by d-amphetamine were significantly correlated with baseline shock rates, but not with baseline response rates. 32 male Sprague-Dawley rats, trained to emit a stable baseline nondiscriminated avoidance behavior, were treated with d-amphetamine. The superiority of baseline shock rates to baseline drug response rates suggests that use of many measures of conditioned behavior may improve accuracy in predicting drug effects on individual subjects.

Medical Research Lab., Chas. Pfizer & Co., Inc.
Groton, Conn.

88 Bindra, Dalbir, & Mendelson, Joseph. Training, drive level, and drug effects: A temporal analysis of their combined influence on behavior. Journal of Comparative and Physiological Psychology, 1963, 56, 183-189.

Chlorpromazine decreased response rate at two higher levels of training but not at the lowest level; methylphenidate decreased response rate at two lower drive levels but not at the highest drive level. The way in which the effect of chlorpromazine and methylphenidate on a trained response (water-reinforced lever-pressing) combine with those of the level of training and drive were studied in male hooded rats. Methylphenidate distracts the animal from the task, but leaves the performance of relevant components of the response unaffected; whereas, chlorpromazine affects response rate primarily through decreasing the speed with which the animal carries out relevant components. Generalization about the basis of differential effects of stimulant and depressant drugs on behavior is suggested.

McGill University
Montreal, P.Q. Canada

89 Sai-Halász, A. The effect of MAO inhibition on the experimental psychosis induced by dimethyltryptamine. Psychopharmacologia, 1963, 4, 385-388.

The usual hallucinatory aspects of the DMT-produced experimental psychosis were not observed in normals when DMT was tested after MAO inhibition with iproniazid. 100 mg. of iproniazid were given daily for four days; two days later DMT was administered to normal volunteers. 2 subjects receiving 0,35-0,55 mg/kg of DMT had no hallucinations, no disturbances in time and space orientation. 5 volunteers on 0,65-0,83 mg/kg experienced 2 phases of effect. The first was similar to the usual DMT psychosis, though less pronounced and the second was characterized by an odd feeling of changed personality, which was considered similar to the schizophrenic "Wahnstimmung." Vegetative signs were only present during the first phase and to a lesser degree than usual with DMT. Pathological state was over in 70 minutes without any additional reaction. Results were held to support theory of a serotonin antagonism in

he mechanism of action of the hallucinogenic rugs.

entr. Inst. f. Nerv. and Ment. Dis.
udapest--Lipótmezo, Hungary

0 Lawes, T.G.C. Schizophrenia, "Sernyl" nd sensory deprivation. British Journal of sychiatry, 1963, 109, 243-250.

henycyclidene produces symptoms akin to early chizophrenia when normal volunteers are un- er ordinary conditions, but the symptoms are onexistent under sensory deprivation condi- ions. 12 aspects of mentation (thinking, ffect, psychomotor activity, time, body im- ge, somatic, irritability, sleep, dreams, ap- etite, delusions and hallucinations) were bserved in 8 male nurses under conditions of ild social stress and demand, conditions of ensory deprivation and social isolation, and ocially isolated conditions without sensory eprivation. Assessment of subjects' reac- ions were then subjectively made using a set f symptoms of early schizophrenia. Results ndicate that the disturbing effects of phen- yclidene are lessened with sensory depriva- ion conditions. Integration of results with heories of the etiology of schizophrenia ere attempted.

ancaster Moor Hospital
ancaster, England

1 McDonald, David G., Stern, John A., & Hahn, William W. Behavioral, dietary, and autonomic effects of chlordiazepoxide in the rat. Diseases of the Nervous System, 1963, 24, 95-103.

Effects of chronic and acute administration of chlordiazepoxide on activity, food, water consumption, body weight, heart rate, and response to stimulation show discrepancies between single and repeated injections as well as discrepancies between this and other reports. Subjects were male albino Holtzman rats. Changes following single versus 5 or 28 daily injections of chlordiazepoxide show 1) resting heart rate of rat receiving 150 mg/kg. higher than controls after single injection, but lower by series of 28 injections; 2) heart rate response bell stimulation decreased by 28 daily injections of 150 mg./kg. while single 50 mg./kg. injections lowered the stabilimeter response to tone stimulation; 3) open field activity wheel running was lowered by single injection; 4) water intake was inconsistently increased by single and 5 daily injections; 5) body weight was significantly increased by single and 5 daily injections and decreased by 28 daily injections. No effect on food intake was noted.

U. S. Navy Medical Neuropsychiatric Res. Unit
San Diego, California

Washington University School of Medicine
Contract

92 Aaronson, Bernard S. The comparative sensitivity of the qualitative and quantitative Porteus Maze scores to drug effects. Journal of Clinical Psychology, 1963, 19, 184-185.

The qualitative scoring of Porteus Mazes shows greater sensitivity than quantitative scoring. Porteus Maze scores of 22 male chronic schizophrenics, given 1 of 2 experimental drugs for one month followed by chlorpromazine showed the variance of qualitative scores differentiated the two compounds while mean differences of qualitative scores and mean and variance differences of quantitative scores did not. Greater sensitivity of qualitative scoring to drug effects suggests that test scoring which represents coding of ongoing behavior may be a better index of psychopharmacological effect than measures oriented to pass-fail criteria.

N. J. Bureau of Research in Neurology and
Psychiatry, Box 1000, Princeton, N.J.

93 Huffman, Warren J., Florio, Aurelio E., Payne, Jobe L., & Boys, Floyd E. The influence of two selected tranquilizers on driving skills. American Journal of Psychiatry, 1963, 119, 885-886.

Normal and double-normal doses of hydroxyphenamate has no significant effect on performance of normal volunteers. 15 male and 10 female student volunteers with no unusual medical history and normal vision were tested to study the behavioral effects of hydroxyphenamate on reaction time, visual acuity, and hand steadiness. Hydroxyphenamate was compared to a placebo and meprobamate. 16 measures were

recorded on 6 occasions. Using the t-test significance, 5 differences were found in 96 comparisons: 1) far visual acuity improved after normal dose of hydroxyphenamate as compared with placebo; 2) visual acuity improved after hydroxyphenamate as compared with meprobamate; 3) with double doses, reaction time slowed with meprobamate compared with placebo; 4) far acuity diminished after hydroxyphenamate as compared with placebo, and 5) near acuity was diminished after meprobamate compared with placebo. Since some statistically significant differences can be expected in a multivariable study, it was concluded that, under conditions of this experiment, hydroxyphenamate had no significant effect on performance.

Department of Health and Safety Education
University of Illinois
Urbana, Ill.

94 Schmidt, H., Jr., & Dry, L. Comparison of phenobarbital and pentobarbital actions upon water ingestion. Journal of Comparative and Physiological Psychology, 1963, 56, 179-182.

Phenobarbital reduces response latency and increases drinking when access to water immediately follows administration of hypertonic saline. 18 male albino rats of the Sprague-Dawley-Holtzman strain were injected with phenobarbital, pentobarbital, or a control solution one-half hour before given hypertonic saline to induce drinking. Phenobarbital reduced response latency and increased drinking whereas pentobarbital had no effect. However, if there is a 5 1/2-hour delay between injection of the saline and access to water, pentobarbital facilitates drinking well above control level. The author concludes that (a) the two drugs differ in their action upon water ingestion; (b) phenobarbital is not an adequate stimulus for drinking; (c) delay between saline administration and drinking introduces some conditions not immediately elicited but not reflected in the volume ingested by comparative controls.

Washington University School of Medicine
St. Louis, Mo.

95 Werboff, J., & Kesner, R. Learning deficits of offspring after administration of tranquilizing drugs to the mothers. Nature, 1963, 197, 106-107.

Meprobamate administered to gravid rats detrimentally altered maze learning ability of offspring whereas chlorpromazine and reserpi did not. 89 gravid albino rats of the Sprag Dawley strain were treated with chlorpromazine (6.0 mg/kg), reserpine (0.1 mg/kg) or meprobamate (60.0 mg/kg) on either 5-8, 11-14, or 17-20 days of gestation. Of the 690 surviving offspring, 10 males and 10 female were selected from each drug and control group. Animals were evaluated on the Lashl III maze with mean and standard deviation f number of trials required to reach criterio of learning. Statistical analysis among th groups was done with the t-test. There wa no significant difference between the reser pine and chlorpromazine groups but the off- spring of the meprobamate treated mother re quired significantly more trials to reach t criterion of learning. Chlorpromazine off- spring weighed more than controls but mepro bamate and reserpine offspring weighed less than controls

Animal Behavior Laboratory, Lafayette Clini
and Wayne State University
Detroit, Michigan

96 Barry, Herbert, Wagner, Sylvia A., & Miller, Neal A. Effects of several drugs o performance in an approach-avoidance confli Psychological Reports, 1963, 12, 215-221.

Chlorpromazine and amobarbital appear to re duce avoidance during tests of performance an approach-avoidance conflict. 12 male alb no rats of the Sprague-Dawley strain were s jects for measuring the avoidance reducing effect of drugs by comparing drug and place performance during a warning signal. Each subject served as its own control. Approac avoidance conflict in an operant-conditioni situation was tested by means of a tone of gradual increasing loudness which signalled that bar presses might be punished by gradu ally increasing shock intensities. During repeated tests, the tone produced a stable decrement in rate of bar pressing. In com- parison to a placebo, amobarbital and chlor promazine increased performance during the warning tone but not in the safe period. Al cohol and LSD decreased performance during the safe period whereas caffeine increased Methamphetamine, deanol, morphine, and coca failed to show any statistically significan effects.

University of Pittsburgh
Pittsburgh, Pa.

Cairncross, Keith D., Gershon, Samuel, Gust, Ian D. Some aspects of the mode of tion of imipramine. Journal of Neuropsy- iatry, 1963, 4, 224-231.

ngle dose and long-term administration of ipramine in conscious and anesthetised ani- ls indicates its antidepressant effective- ss in modifying excessive cholinergic ac- vity. Anticholinergic effect at the syn- tic or neuronal level makes imipramine dif- r widely from the MAO inhibitors which ise central catechol amine levels and in- ce a high level of cortical activity. Ef- ct of imipramine on the nictitating mem- ane, on the cardiovascular responses to ogenous neuromediators, and on the isolated s deferens of the guinea pig show imipra- ne to have atropinelike properties.

ychopharmacology Unit,
iversity of Melbourne
ctoria, Australia

8 McGeer, Patrick L. Central amines and xtrapyramidal functions. Journal of Neuro- sychiatry, 1963, 4, 247-250.

fforts to establish relationships between entral amines, psychoactive drugs and the unctioning of the motor system show the ecessity of using more refined techniques efore significant conclusions can be drawn. uthor points out that drugs such as reser- ine and certain phenothiazines which produce xtrapyramidal effects similar to parkinson- sm are strong blockers of the actions of atecholamines and serotonin but are weak ntihistaminics, whereas drugs that counter- ct parkinsonism are generally anticholiner- ic, antihistaminic, or both. In a clinical rial DOPA failed to produce results in pa- ients suffering from severe extrapyramidal eactions caused by reserpine; but diphen- ydramine was effective. In rats, thiopro- erazine-induced rigidity was only partially vercome by measures designed to increase he weight of the catecholamine-serotonin ystem. Reversal of the thioproperazine ef- ect did occur with diphenhydramine and di- thazine. In reserpinized rats, DOPA and 5- TP alone were insufficient to reverse the ffect of reserpine. Diphenydramine was not effective either.

Kinsmen Laboratory of Neurological Research
University of British Columbia,
Vancouver, B. C., Canada

BIOCHEMISTRY AND CHEMISTRY

99 Forrest, Irene G., Wechsler, Magdelena Berger, & Sperco, Joseph E. A comprehensive method for the determination of urinary chlorpromazine and its oxidative metabolites. American Journal of Psychiatry, 1963, 120, 44-48.

Urinary chlorpromazine and its metabolites can be determined by quantitative absorption on Dowex 50 W-X4 cation exchange resin. Total urinary chlorpromazine or fractions thereof can be determined making the method advantageous over other quantitative procedures. Polar, intermediary oxidative and conjugated metabolites constitute 80 percent of the urinary drug. Recoveries range from 88 percent to 97 percent. One half of daily drug doses were found to be excreted in urine.

Biochem Research Lab.
V.A. Hospital
Palo Alto, Calif.

100 Mennear, John H., Bradley, C. Allen, & Miya, Tom S. A study of the chlorpromazine induced decreased liver glutathione reaction. Proceedings of the Society for Experimental Biology and Medicine, 1963, 112, 199-202.

Decreases in liver glutathione levels induced by chlorpromazine in female Holtzman rats are dependent on adrenal medullary and cortical hormones, but not on pituitary hormones. Adrenalectomy blocks the liver glutathione lowering action of a single dose of chlorpromazine. Hypophysectomy does not effect these levels, but stress or chlorpromazine injection does have this effect in hypophysectomized rats. Chlorpromazine does not lower liver glutathione levels in rats pretreated with Amphenone B. In hydrocrotisone-maintained adrenalectomized rats epinephrine lowers liver glutathione levels, but chlorpromazine does not.

Hazelton Laboratories,
Falls Church, Va.

101 Cochin, Joseph, & Daly, John W. The use of thin-layer chromatography for the analysis of drugs. Identification and isolation of phenothiazine tranquilizers and of antihistaminics in body fluids and tissues. Journal of Pharmacology, 1963, 139, 160-165.

A method for identifying phenothiazines and antihistamines in body fluids by thin-layer chromatography is described and its effectiveness was demonstrated with human subjects. Rf values and color reactions for 18 phenothiazines, 8 sulfoxides, 18 antihistaminics, and chlordiazepoxide are given. Applicability of the technique was demonstrated by giving clinical doses to patients and volunteers once the compounds or their metabolites were detected and identified in urine. The method involves extraction of the drug at pH 9.0 from blood or urine into ethylene dichloride containing 10 percent isoamyl alcohol. The extracting solvent is evaporated in vacuo and the residue is dissolved in a small volume of ethanol, and is then spotted on thin-layer chromatoplates.

Boston University School of Medicine
Boston 18, Massachusetts

102 Yates, Celia M., Todrick, A., & Tait, A. C. Aspects of the clinical chemistry of desmethylimipramine in man. Journal of Pharmacy and Pharmacology, 1963, 15, 432-439.

Evidence does not support the hypothesis that failure of depressed patients to respond to antidepressants is due to individual failure of absorption. 6 female patients suffering from symptoms of depression received DMI orally in doses of 75 mg. for 3 days, 100 mg. on the fourth day, 125 mg. on the fifth and 150 on subsequent days. Blood plasma levels of DMI were followed over four weeks. Results suggested that there was an inverse relation between mean plasma DMI concentration and the weight of the patient. Two to 3 weeks of DMI treatment was necessary before blood platelet 5-hydrotryptamine was significantly lowered whereas an improvement in symptoms took place earlier. A method for the fluoremetric estimation of desmethylimipramine in plasma is described.

Crichton Royal, Dumfries, Scotland

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Bethesda, Maryland 20014

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PSYCHOPHARMACOLOGY ABSTRACTS

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REVIEWS, SUMMARIES, BIBLIOGRAPHIES, AND GENERAL ARTICLES AND BOOKS

103 Wada, Juhn A., Kumashiro, Hisashi, Seino, Masakazu, Wrinch, John, & Hill, Donald. Blocking of 5-hydroxytryptophan induced behavioral and electrographic changes by atropine and eserine. In: Recent Advances in Biological Psychiatry. Volume 5. New York: Plenum Press, Inc., 1963, 161-174.

Recent investigations of the effect of neurohumoral agents on cerebral epileptogenic electrical activity and other variables are reviewed. Blocking by atropine is summarized as follows: Agents or procedures which have been shown to elevate brain serotonin levels were most effective in activating epileptogenic cerebral electrical activity. Such activation was at least partially blocked by atropine. Behavioral and electrographic changes in normal cats, monkeys, and man, as well as subjective changes in man following the administration of 5-HTP were blocked or markedly reduced. Cortical excitability following topical application of acetylcholine in cats was modified. It is suggested that 5-HTP sensitizes the cholinergic neurons through which the central action of 5-HTP may be mediated, and that the blocking action of atropine may be affected by dampening such sensitivity. Eserine minimized the 5-HTP effect in avoidance-trained cats but accentuated it in approach-trained monkeys. It is postulated that central action of 5-HTP is competitive with the increased level of brain acetylcholine in avoidance behavior. The differential effect of 5-HTP-eserine in avoidance and approach behavior is cited as suggestive evidence of different neurochemical mediating mechanisms.

(No address)

104 Kline, Nathan S. Psychiatry in Indonesia. American Journal of Psychiatry, 1963, 119, 809-815.

Indonesia has only 32 trained psychiatrists to care for its population of 97,000,000 people. Psychiatrists have to work for the government each morning, but may indulge in private practice during the afternoon and evening hours. Financial recompense is abysmally low. Facilities are deplorable and only 27 hospitals have any sort of facilities for treating the mentally ill. Diagnostic categories include a full spectrum of disorders, such as schizophrenia, manic-depressive psychosis, hysteria, mania, melancholia, general paresis, epilepsy, etc. Lengthy waiting lists precede hospitalization and only patients who can afford their own drugs receive chlorpromazine (150 mg/day) or reserpine (3 mg/day). Some patients receive ECT about 3 times a week. As there are no electroshock machines, convulsions are produced by placing electrodes on either side of the head and then plugging in and out of a wall circuit. Facilities for laboratory examinations are also extremely limited. Unique types of psychiatric disorders observed include running amok, and diguna-guna, which is probably a type of anxiety pseudopsychosis. It is clearly impossible to furnish an adequate number of psychiatrists or hospital beds for Indonesia in the immediately foreseeable future.

Rockland State Hospital
Orangeburg, N. Y.

105 McCormick, W. O. Tranylcypromine. Lancet, 1963, 7273, 167. (Letter)

Lees and Burke (1963), in an uncontrolled study, treated 60 heterogenous patients, varying from tension and anxiety to myasthenia gravis with tranylcypromine, for 8 months and achieved an antidepressant effect in 75 percent of the cases. Tranylcypromine was suggested as an effective antidepressant, despite the fact that conclusions were drawn from uncontrolled trials. The 75-percent rate of amelioration has been approximated in similar illnesses with remedies such as CO_2 inhalation, intravenous acetylcholine, chlorpromazine, and meprobamate. Criticism is predicated upon the need for further evaluation of the MAO inhibitors, which have serious side effects and are potentially dangerous, before they are placed

in the hands of those who might prescribe them in preference to simple symptomatic remedies for psychic syndromes.

Bethlem Royal Hospital
Beckenham, Kent
England

106 Siegler, Peter E., Mapp, Yolanda, Shulkin, Mark W., Ducanes, Arnold D., Bodi, Tibor, & Nodine, John H. Depression in medical practice. Postgraduate Medicine, 1963, 33, 159-164.

Depressive syndromes encompass three distinct entities: psychotic, psychoneurotic, and drug-induced depressions which are treated medically with drugs, supportive measures, and environmental changes, or psychiatrically with psychotherapy, psychoanalysis, drugs, ECT or combinations of these components, all therapy being based upon the needs of the individual. Depression is currently alleviated by means of the psychic energizers, which include sympathomimetics (dexamphetamine), marginal sympathomimetics (methylphenidate and pipradrol), MAO inhibitors (iproniazid, nialamide, isocarboxazid, tranylcypromine), and other compounds such as imipramine and amitriptyline. Psychic energizers are evaluated by plotting a dose-response curve for each patient and a similar curve for the predominant side effect obtained at each dose level, after which the useful dose range is related to the actual clinical improvement as well as the incidence of significant side effects. Alterations in mood are then determined with projective techniques like the Rorschach, TAT, MMPI, and Clyde Mood Scale; psychomotor performance is evaluated by tests of reaction time, tapping rate, the pursuit rotor, and digit substitution tests. An individual approach is essential to combine the clinician's knowledge with his experience in the available therapeutic methods.

Hahnemann Medical College and Hospital
Philadelphia, Pa.

107 Ayd, Frank J., Jr. Response to antidepressants. Lancet, 1963, 7274, 225. (Letter)

Depressed patients will exhibit similar responses to MAO inhibitors or imipramine-like antidepressants in succeeding illnesses. Furthermore, close relatives who suffer from depressive syndromes will react to these drugs in an analogous fashion. In view of this information, the clinical history of a given patient should include full elucidation of similar syndromes evinced by his close relatives. Familial components provide vital guides to the prognosis and treatment of depressive illness.

Baltimore, Maryland

108 Needham, C. D. Approved names of drugs. British Medical Journal, 1963, 5326, 330. (Letter)

A plea is tendered for a systematic overhaul of the currently cumbersome polysyllabic system of pharmaceutical nomenclature which is rife with discrepancies between official and proprietary names. Apparently a considerable degree of difficulty accompanies memorizing chemical designations such as tranylcypromine (Parnate), chlordiazepoxide (Librium), trifluoperazine (Stelazine) and isocarboxazid (Marplan). Although the generic names offer clues to the molecular structure, most physicians lack the requisite chemical proficiency to utilize such information adequately, and would much prefer to remember euphonious official names rather than plunge into the present morass of multiple proprietary designations. Extensive revamping would undoubtedly result in a collection of minutely detailed chemical names paralleled by vastly simplified proprietary names.

(No address)

109 British Medical Journal. Procaine for depression. British Medical Journal, 1963, 5326, 319. (Letter)

Extravagant claims emanating from Rumanian clinicians with respect to the therapeutic efficacy of procaine, a well-known local anesthetic, as a panacea with widespread beneficial effects in the elderly, have been completely disproved by several clinical trials conducted in Great Britain. The hypothesis that procaine is valuable in the treatment of endogenous depression or behavioral disorders in children should also be regarded with the utmost skepticism until well-controlled clinical trials provide corroboration. No such evidence is currently in existence.

British Medical Association
Tavistock Square
London W C. 1, Great Britain

110 Green, D. M., & Krueger, R. F. Sex differences in drug effects. Federation Proceedings, 1963, 22, 543. (Abstract)

The nature and incidence of symptoms in men as compared with women before and after the administration of acetylsalicylic acid, caffeine, phenobarbital and hydroflumethiazide were studied among groups of well professional personnel and prisoners and among patients suffering from various medical diseases. Information was obtained through questions as to the presence or absence of a variety of symptoms in the medical history and followup examinations. The nature of the effects reported after treatment was similar in the male and female groups. The incidence or intensity of these effects in a majority of instances (but not in all) was higher in women. The difference was more marked among well subjects than in patients. Studies with placebos suggested that this sex difference could be attributed in part to differences in pretreatment condition and in responsiveness to the act of administering a drug. Nevertheless, the specificity of some of the reported effects indicated greater sensitivity to the drug per se. In acetylsalicylic acid, the difference in sex sensitivity could be correlated with the development of higher serum salicylate levels following equal metric doses.

Grove Lab. Inc.
St. Louis, Mo.

111 Medical Journal of Australia. International names for drugs. Medical Journal of Australia, 1963, 131, 479. (Editorial)

In British practice most drugs have at least three names: the chemical name, the approved name and one or more proprietary names. Wide discrepancies exist, however, between British and American pharmacopoeial names (e.g., adrenaline British versus epinephrine American), a fact which creates much confusion. Eventually, it is hoped that the lists of international nonproprietary names published by WHO (e.g., International nonproprietary names for Pharmaceutical Preparations: Cumulative List 1962) will be adopted by national authorities as the universally accepted standard. The thalidomide disaster has made the medical profession acutely aware of the need for alleviation of the chaotic condition which now characterizes pharmaceutical nomenclature.

Australian Medical Association
Sydney, Australia

112 Medecine et Hygiene. Le Gouvernement de Grande-Bretagne lance un programme de tests des medicaments. (The government of Great Britain launches a program of drug testing.) Medecine et Hygiene, 1963, 593, 400. (French)

All new drugs manufactured in or imported into Great Britain must be approved by a Committee on Drug Safety nominated by the Ministry of Public Health; this committee will examine about 300 new products a year. New legislation has been instituted following the thalidomide tragedy. Three subcommittees will handle 1) toxicity, 2) clinical testing, and

3) marketing of the drug. The Committee is under the direction of Lord Cohen of Birkenhead.

22, rue Michell-du-Crest
Geneva, Switzerland

113 Medecine et Hygiene. Tests de toxicite pour les nouveaux medicaments. (Toxicity tests for new drugs.) Medecine et Hygiene, 1963, 593, 404-405.

In the first stage of drug testing, pharmacologic effects, determination of lethal and toxic doses, and chronic and subacute effects in laboratory animals are briefly noted and comment passed concerning growth. Clinical testing is then outlined and it is stressed that substances completely innocuous to one species may produce disastrously toxic effects in another species. Clinicians must realize that events following the administration of a new drug cannot be predicted from experiences in animal pharmacology.

22, rue Michell-du-Crest
Geneva, Switzerland

114 Medecine et Hygiene. L'esperimentation des medicaments en URSS. (Drug experimentation in the USSR.) Medecine et Hygiene, 1963, 593, 481.

Drug experimentation in the USSR is under the Pharmacological Committee of the Ministry of Public Health. Pharmacology and clinical trials are operated under this committee. The State Committee of the Pharmacopeia of the Ministry of Public Health decides on the technical conditions of preparations, controls manufacture, and expedites information on the administration of pharmacies in the various republics. The Pharmacologic Committee publishes informational notes on its activity relating to new drugs.

22, rue Michell-du-Crest
Geneva, Switzerland

115 Medecine et Hygiene. L'experimentation des medicaments aux Etats-Unis. (Drug experimentation in the United States.) Medecine et Hygiene, 1963, 593, 481.

The history of drug control in the U. S., including notes on the FDA and Senator Kefauver's investigations, is briefly noted. Collaboration of the pharmaceutical industry, university clinicians, and the FDA may end the present period of crisis and favor the progress of therapy.

22, rue Michell-du-Crest
Geneva, Switzerland

116 Medecine et Hygiene. Le controle des medicaments en Angleterre. (Drug control in England.) Medecine et Hygiene, 1963, 593, 400. (Editorial)

The British plan for the control of new drugs already finds great opposition in the country. The Pharmaceutical Society of Great Britain which has 29,000 members, estimates that the adopted plan is not sufficient to prevent reoccurrence of a tragedy similar to that of thalidomide. They consider it unsatisfactory to confer control responsibility on the drug firms, while the governmental agency responsible for drug evaluation is not itself sufficent. With new drug developments in the tranquilizer and contraceptive areas, not only medical but social problems are also involved.

22, rue Michell-du-Crest
Geneva, Switzerland

117 Glueck, Bernard C. Research in mental hospitals. Mental Hospitals, 1963, 14, 93-96.

Advantages and problems concomitant with the extension of research activities from isolated laboratories into hospitals and clinics are examined. Advantages are briefly listed as: 1) easy interchange of

ideas between research workers and clinical staff, 2) discussion of practical problems in applying research to treatment programs, and 3) opportunities for researchers to capitalize on clinical hunches. On the other hand, problems are more fully indicated and discussed. They include: 1) research necessary to determine the suitability of a drug for clinical trial, 2) balancing of severity of illness against risk of untoward effects, 3) impact of use of placebos on attitudes, 4) source of research funds whether or not from patient-care funds, 5) pressure leading to emphasis on applied rather than basic research, and 6) impact of research studies on ward personnel, particularly nurses. The point of view which argues that the need for clinical trial of drugs in psychiatric illness is not as urgent as that for widespread malignancy, for example, is challenged. The recent stand taken by insurance companies who have held that they are not responsible in negligence, malpractice, and damage suits, if the drug in question has not been approved by the Food and Drug Administration, is suggested as resulting in termination of clinical drug research in many institutions, both state and private.

Institute of Living
Hartford. Connecticut

118 Unger, Sanford M. Mescaline, LSD, psilocybin, and personality change. A review. Psychiatry Journal of Interpersonal Relations, 1963, 26, 111-125.

Drug experience associated with mescaline, LSD, and psilocybin, with particular attention to extra-drug variables influencing personality change, is reviewed. With respect to the equivalent action of the three drugs, it is pointed out that subjective effects are presently adjudged similar, equivalent, or indistinguishable and that cross-tolerance does in fact develop. When extra-drug variables are controlled, there is no reaction distinctively associated with any of the three. On the other hand, attention is called to invariant drug reactions which include alterations in visual experience such as changes in perception of form, light, and color; depersonalization or body image distortion; and retrospective impressiveness of the drug experience. These invariants do not seem to approximate delirium for non-psychotic subjects. The history of the "psychotomimetic" label is given with a discussion of its appropriateness. Though few controlled investigations of effects of extra-drug variables are available for review, the reviewer feels that it is clear from the systematic variability of reported reactions, that factors other than specific pharmacologic action or personality of the subject are at issue. Hundreds of cases are cited pro and con regarding willingness to repeat the drug experience. Psychoanalysts report patients reliving childhood experiences, Jungians found their patients had "transcendental" experiences, while Harvard students grappled with age-old paradoxes. The environmental setting and specifically the orientation and expectation of the therapist or experimenter not only influence drug experience, but the positive or negative character of the experience can be systematically directed. Therapeutic implications are summarized and the phenomenon of drug-associated rapid personality or behavior change is discussed in detail. Examples of rapid behavior transformations not drug-associated are presented for comparison and explanatory concepts are reviewed.

NIMH Laboratory of Psychology
National Institutes of Health
Bethesda, Maryland, 20014

119 Robin, A. A. The effect of tranquillizers on some aspects of the treatment of long stay patients. American Journal of Psychiatry, 1963, 119, 1076-1081.

Tranquilized long-stay patients when compared to nontranquilized patients do not have a better prospect of discharge. A retrospective study of a long-stay population from 1952-58 at Runwell Hospital in Essex, England, was made. A selected number of these patients were exposed to tranquilizers, the intent was to compare them with similar long-stay patients who did not receive tranquilizers. Comparisons were made in regard to time of discharge and general ward behavior. Conclusions

were: 1) patients chosen for tranquilizers were those with the best outlook as far as discharge is concerned; 2) tranquilized patients when compared to the nontranquilized patients did not have a better prospect of discharge; 3) tranquilization did not alter the chance of readmission of discharged long-stay patients; and 4) ward behavior was notsignificantly influenced by tranquilizers. It is concluded that tranquilizers do not produce better results than nursing care and occupational therapy for long-stay patients.

Runwell Hospital
Nr. Wickford
Essex, England

120 Kurland, Albert A. Implication of Indoklon for psychiatric research. Journal of Neuropsychiatry, 1963, 4, 173-177.

A review of the developments which have taken place in the study of Indoklon as a pharmacoconvulsive agent and its comparison with ECT has brought researchers to a point where further considerations of the strategy in the study of this compound seem pertinent. In initial investigations of Inkoklon administered as an inhalant convulsant, there appeared to be no particular advantage in using this agent over ECT from the standpoint of clinical results and psychometric and electroencephalographic changes. The preparation of a 10 percent solution of Indoklon for intravenous used produced encouraging chemical results and matched the smoothness of ECT in its administration. The most satisfying clinical and psychometric results were obtained in combining Indoklon and ECT. The availability of two types of convulsive agents, namely ECT and Indoklon, should provide further insight into the possible differences of these agents when used in combination with psychotropic drugs. There is much support for using the combination of psychotropic drugs with convulsive therapy on schizophrenic reactions in order to achieve greater degrees of improvement and a decrease in length of hospitalization. The data presented here support the use of Indoklon in convulsant therapy as a safe alternate to ECT.

Department of Mental Hygiene
State of Maryland
Baltimore, Maryland

121 Modell, Walter. Seminar on the clinical evaluation of drugs. Clinical Pharmacology and Therapeutics, 1963, 4,371-380.

The problems of selecting the most appropriate human subjects for controlled studies are often ignored. Examination of the problems involved in design of investigations of drugs in man indicate that there is no routine approach which provides meaningful answers in all cases. Appropriat control of the experiment in man is especially elusive. Each case has to be considered separately. It is suggested that with the increasing recognition of the need for controlled studies in man, some aspects of the problems have been generally recognized and better handled than previously.

Department of Pharmacology
Cornell University Medical College
New York, New York

122 Blumenthal, Lester S., & Fuchs, Marvin Current therapy for headache. Southern Medical Journal, 1963, 56, 503-508.

Pathophysiology of headaches can be modified by drugs, with the patient able to handle many of the attacks himself. The following therapies were evaluated in treating and preventing headaches resulting from various causes: orphenadrine citrate benefited posttraumatic, cervical spine arthritic, and primary tension headaches; ergotamine tartrate and related compounds, and methylisoocentylamine HCl, benefited headaches of primary vascular origin; meprobamate, Plexonal, Fiorinal, thioridiazine HCl, chlordiazepoxide were effective as relaxants in preventing headaches. UML-491 produced side effects of nausea, arm and leg spasm, and painful

drawing in some patients but benefited others. UML-491 combined with cyproheptadine produced no side effects and was more beneficial to some than UML-491 alone. Carisoprodol relieved anxiety or insomnia. Hydroflumethiazide (Saluron) alone or with phenoltoloxamine was effective with premenstrual tension headache. Phenylethylhydrazine (Nardil) did not exceed the placebo effect in relieving headaches resulting from depression but etryptamine acetate (Monase) was effective. Posttraumatic syndromes were successfully treated by the injection of special proliferating agents at the point of insertion of the involved ligaments at the base of the skull.

Washington, D. C.

123 Schiele, Burtrum, C. Antidepressants: comparison of clinical effects in anergic schizophrenia and the depressed states. Annals of the New York Academy of Science, 1963, 107, 1131-1138.

Antidepressants have similar spread of effects in depressive disorders and anergic schizophrenia, with the non-MAO inhibitors being more efficacious than the MAO inhibitors, but neither being as effective as electroshock therapy. The comparative effects of antidepressants in depressed patients and in anergic (chronic, institutionalized) schizophrenics are presented after studies with various antidepressants are reviewed. The antidepressants in question were classed as follows: (1) hydrazine MAO inhibitors (iproniazid, isocarboxazide, nialamide, phenelzine), (2) nonhydrazine MAO inhibitors (pargyline, tranylcypromine), (3) non-MAO inhibitors (amitriptyline and imipramine). The conclusions were (1) that antidepressants in general have a similar spread of effects in depressive disorders and anergic schizophrenia, in that they all tend to be mood elevators and psysiologic energizers, and that these effects are more pronounced in the more depressed patients (better organized) than in schizophrenic patients (more disorganized). The author ranks treatments in order of their efficacy with depressive symptoms as follows: most effective (1) electroshock therapy, (2) non-MAO inhibitors, (3) MAO inhibitors, but notes that in most classic schizophrenics, drugs are usually more effective than EST.

University of Minnesota Hospital
Minneapolis, Minnesota

124 Leck, Ian, & Smithells, R. W. The ascertainment of malformations. Lancet, 1963, 7272, 101-103.

In order to diminish the possibility of future delays, should a situation analogous to the thalidomide tragedy arise, studies of the incidence of malformation in large populations are needed. Such studies are required: (1) in the planning of medical and educational services as a source of advance knowledge of the number of children likely to need special care and (2) in etiological research to detect epidemics at a relatively early stage and explore the relationship of incidence to events in early pregnancy, race, locality, and other environmental and genetic variables which may be of etiological importance. Existing studies on the incidence of malformations deal with the size of the population (national studies, state surveys, local inquiries, and hospital series) and the timing of the decision to conduct a survey relative to the birth of those surveyed. Local inquiries should be contemplated in terms of cases to be included, sources of information, particulars required, and methods of analysis.

University of Liverpool
Liverpool, Great Britain

125 Rassidakis, N. C., Lykas, Ch., Papadakis, E., & Kafatou, A. A followup study of schizophrenic patients: relapse and re-admission. Bulletin of the Menninger Clinic, 1963, 27, 33-40.

A strong association was found to exist between the age at onset of schizophrenia

and the time of relapse in a group of 52 patients studied. This investigation was a followup study of schizophrenic patients at the State Mental Hospital in Athens, Greece, involving 52 discharged mental patients. The purpose of study was to find out what had happened to each patient after discharge and to discover what factors contributed to the patient's continued recovery or to his relapse and readmission to the hospital. The data presented in the study revealed (1) a statistically significant association existing between the age of onset of schizophrenia and the time of relapse; early relapse appearing closely connected with an early onset of the illness and vice versa; (2) an association between marital status and performance level of patients on the one hand and time of relapse on the other; (3) an absence of any correlation existing between time of relapse and the kind of treatment during hospitalization.

(No address)

126 Katz, Martin M., & Cole, Jonathan O. A phenomenological approach to the classification of schizophrenic disorders. Diseases of the Nervous System, 1963, 24, 1-8.

An attempt is made to classify schizophrenic patients empirically according to behavioral dimensions for the purpose of extending information on what schizophrenic patients are like on a behavioral level and to determine whether these classifications are predictive with regard to treatment response. Phenomenological and anamnestic building blocks on which current diagnosis rests were reexamined to see whether more coherent diagnostic groupings could be extracted from readily available clinical data. The clinical data overhaul was in the nature of quantifiable descriptions of patient symptoms and social behavior. Noting that the present instruments for turning out this information were designed for raters with professional training who were influenced by traditional habit in thinking about psychopathy, the authors turned to what they felt was a more objective-reliable source, the close relative, for detailed data on symptoms and social behavior. Acute schizophrenia was selected as the important diagnostic group for study. Each close relative was interviewed at admission and an inventory of the patient's symptoms and social behavior was administered. The inventory was one of a set of scales devised by senior author (Katz) for assessment of a patient's adjustment in the community. An attempt to arrive at "patient types" was achieved from a random sample of 24 patients selected from an original group of 100 newly admitted acute schizophrenics at Spring Grove State Hospital, Md. This provided for a set of relatively homogenous behavioral items which, when interpreted, were used to describe specific aspects of a patient's behavior. It was hoped that these profiles of "patient types" could be utilized in predicting response to drug treatments.

Psychopharmacology Service Center
Research Grants and Fellowships Branch
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Bethesda 14, Md.

127 Haertzen, Charles A., Hill, Harris E., & Belleville, Richard E. Development of the Addiction Research Center Inventory (ARCI): Selection of items that are sensitive to the effects of various drugs. Psychopharmacologia, 1963, 4, 155-166.

The ARCI contains demonstrated "drug-sensitive" questions and items which may delineate to some extent schizoid and psychopathic characteristics. The report summarizes the methods used in developing the 550-item ARCI. Sentence completion, alternative stem, paired comparison tests, and word and drug association tests were given under drug and "no-drug" conditions. Items on sensation, perception, anxiety and mood, bodily symptoms, and activity level were changed more often than those

concerning personality characteristics, occupational interest, general attitudes, or philosophy of life. A considerable number of items suggested behavioral abnormalities. Results also indicate that the effectiveness of specially designed tests chiefly depends upon assessment of the "activity-sedation" continuum and changes in motivation, alterations in mood, sensation, and perception, and in reportable psychological processes.

NIMH Addiction Research Center
PHS Hospital
Lexington, Ky.

128 Hill, Harris E., Haertzen, Charles A., Wolbach, Albert B., Jr., & Miner, Edward J. The Addiction Research Center Inventory: Appendix I. Items comprising empirical scales for seven drugs. II. Items which do not differentiate placebo from any drug condition. Psychopharmacologia, 1963, 4, 184-205.

The listing of items of the ARCI is presented as an appendix to other papers that describe the development and initial use of this instrument for assessing subjective effects of drugs. The items are classified according to their effectiveness in discriminating drug effect from the placebo condition. Two scales were developed for each of these conditions with the following drugs: morphine, amphetamine, pentobarbital, alcohol, LSD-25, pyrahexyl, and chlorpromazine. Questions concerning attitudes toward individuals and institutions, and questions on philosophy of life are generally not in the significantly altered category. Questions on sensations, perception, bodily symptom, moods, drives, attitudes toward taking the test and motivations are sensitive to drug effects.

NIMH Addiction Research Center
PHS Hospital
Lexington, Kentucky

129 Hill, Harris E., Haertzen, Charles A., Wolbach, Albert B., Jr., & Miner, Edward J. The Addiction Research Center Inventory: standardization of scales which evaluate subjective effects of morphine, amphetamine, pentobarbital, alcohol, LSD-25, pyrahexyl chlorpromazine. Psychopharmacologia, 1963, 4, 167-183.

Former drug addicts, under a number of drug conditions, were used to standardize the ARCI for assessing subjective drug effects and personality characteristics. Except alcohol, which was given orally, the drugs and placebo were administered both orally and intramuscularly to the 219 male post-addict prisoners who volunteered to serve as subjects. The ARCI was administered under "no-drug" placebo, and under various doses of morphine, pentobarbital, chlorpromazine, LSD-25, amphetamine, pyrahexyl, and alcohol. Items were chosen to comprise each drug scale that discriminated the drug from placebo; the no-drug-placebo comparison produced a placebo scale. Nonsignificant differences were combined for standardizing all scales. Validity generalization, dose effect, and retest studies showed that the drug scales possessed a high degree of reliability and validity. The placebo scale lost discrimination entirely in the validity generalization group.

NIMH Addiction Research Center
PHS Hospital
Lexington, Kentucky

130 Journal of the American Medical Association. Council on Drugs. New drugs and developments in therapeutics. Journal of the American Medical Association, 1963, 183, 469-470.

Chlordiazepoxide (Librium Hydrochloride), hydroxyphenamate (Listica), emylcamate (Striatran), mephenoxalone (Trepidone, Tranpoise, Lenetran), buclizine hydrochloride (Softran), and chlormezanone (Trancopal) are discussed regarding their therapeutic value. These six "minor"

tranquilizers are useful in the oral treatment of mild symptoms of tension and anxiety. None is effective in psychosis treatment. All have drowsiness as a sife effect. They seem to be no more useful than older well-established drugs of similar therapeutic range and safety ratio. Phenothiazines or monoamine oxidase inhibitors as well as other psychotropic agents, known to potentiate the action of other drugs, should be avoided in concomitant administration.

American Medical Association
Chicago 10, Illinois

131 Nagle, David R. The use of anesthetic agents in psychiatry. Anesthesiology, 1963, 24, 91-94.

The use of anesthetic drugs may produce temporary remission in psychotic patients, while in psychoneurotic patients alteration of consciousness is produced, similar to that resulting from hypnosis, to improve psychic functioning. Slow intravenous administration of amobarbital sodium has been useful in differentiating neurotic from psychotic depressions. Various psychiatric categories require different amounts in mg/kg to produce desired changes. Ether or chloroform were used in functional psychoses as well as in neuroses. Intravenous ether has been used for depressive psychoses. In neuroses, ether was administered via open drop mask. Atropine (32-200 mg) and scopolamine (5-50 mg) are used as toxicity treatment for schizophrenia. This therapy seems similar to insulin-coma therapy in behavioral aspects. Intravenous barbiturates are also used in neurosis therapy. Among uncovering techniques for neuroses are narcoanalysis and abreaction. A little known technique, narcoplexis, is of particular interest to those anesthesiologists who use supplementary barbiturates with regional anesthesia. Methamphetamine (15-40 mg) i.v. has produced an improved altered state of consciousness but its side effects limit its usefulness for the psychiatrist. Nitrous oxide, trichloroethylene, ether and chloroform mixtures, chloroform, hydroxydione, and methohexital are also producing desired alteration of consciousness. Carbon dioxide has therapeutic effectiveness when coma, with accompanying convulsive movements, is deliberately produced. Anesthetics used as psychopharmacological agents have not been thoroughly explained as to their mechanism of action. (41 refs.)

Good Samaritan Hospital
Lexington, Kentucky

132 Bowman, Karl M., & Engle, Bernice. Geriatrics. American Journal of Psychiatry, 1963, 119, 652-654.

A review of studies on psychological and physiological factors in aging indicate a need for research in geriatrics. Biophysical and biochemical changes and psychological factors contribute to the impairment of capacities in elderly people. Phenothiazines were beneficial to aged paranoid patients, whereas nialamide and ethyltryptamine were effective in depressed subjects. The authors state that a number of reports concern improvement after psychopharmacological therapies. (10 refs.)

University of California
San Francisco, California

133 Moriarity, John D. Pitfalls in the clinical evaluation of psychotropic drugs. Diseases of the Nervous System, 1963, 24, 36-37.

In evaluating the effects of psychotropic drugs, especially in private practice, "contaminants" such as simultaneous administration of other forms of psychiatric treatment, spontaneous fluctuation in the course of the disorder, and extratherapeutic forces in the patient's life must be considered. Properly designed with a

reasonably homogenous sample of adequate size, double-blind placebo controls, and proper randomization can partially eliminate bias of both the therapist and the patient. Rating scales seem less satisfactory than expert clinical judgment and administration of psychological tests is considered impractical. (4 refs.)

6753 Hollywood Boulevard
Los Angeles 28, California

134 Freedman, Daniel X. Psychotomimetic drugs and brain biogenic amines. American Journal of Psychiatry, 1963, 119, 843-850.

It is suggested that endogenous brain amines such as serotonin and norepinephrine are not only responsive to psychotomimetic drugs such as LSD-25 and its congeners but also to some factors of stress caused by excessive activation or demand. This paper reviews some of the studies on animals (rats, rabbits, dogs) and humans, which show that psychotomimetic drugs have more than one action and more than one site of action. Some psychoactive compounds such as reserpine and MAO inhibitors were found to increase or decrease brain amino levels. These effects were correlated with patterns and levels of excitment. Some of the psychotomimetic drugs like LSD-25 can also influence the brain amine metabolism, whose governing intrinsic mechanisms can affect the chemical behavioral and automatic response to the drug. It is pointed out that LSD-25, as well as related drugs such as mescaline, ALD, MLD, Psilocybin, and BOL cause a rise in serotonin and a decrease in norepinephrine levels in the whole brain of the animal tested. In human schizophrenics the behavioral and autonomic response was different. If LSD-25 were given 2 days after reserpine, LSD-25 caused prolonged and toxic reactions. It induced binding of serotonin in particular; its effect on amino levels was reduced or enhanced with chlorpromazine or BOL. It also stimulated repletion after reserpine. If endogenous amine mechanisms are chemically or genetically impaired, physiologic function could be altered under stress. These changes could reflect an incidental rather than a necessary response to the drug. (29 refs.)

Yale University
School of Medicine
New Haven, Connecticut

135 Bartholomew, A. A. Problems of addiction. Medical Journal of Australia, 1963, 9, 315-318.

The concept of drug dependency is invaluable for ordinary clinical use and relieves the physician of the need to indulge in sophistry to determine whether a patient is addicted, habituated or something in between, with respect to a given substance. Certain psychoneuroses predispose toward the modern tendency to prescribe a tranquilizer or antidepressant to ward off any untoward effects secondary to even the most minor commonplace ailments. Many of these drugs produce dependency, and fledgling members of the medical profession are almost invariably unaware of the harm that may ensue from substituting such drugs for an acceptable treatment regimen, designed to ameliorate the organic dysfunction rather than pander to the psychosomatic aspects of the patient's condition. It is imperative that physicians acquire a higher degree of knowledge and understanding on the subject of pharmacology. Psychotropic drugs should be doled out with a far less lavish hand. New drugs should be distributed with caution, and only after their properties have been exhaustively studied. (40 refs.)

Alexandra Clinic
Melbourne, Australia

136 Suarez, Manuel Velasco, Cabildo, Hector M., Ruiz, Carlos Tejada, & Nieto, Dionisio. Present status of psychiatry in Mexico. American Journal of Psychiatry, 1963, 120, 160-163.

A brief historical survey of psychiatric

services in Mexico is presented with emphasis on recent developments. It is pointed out that Mexico was the first country on the continent to have an institution devoted to the care of mental patients. Services since its founding in 1566 are generally discussed. Percentage figures of diagnostic categories in 10-year intervals since 1910 are presented. The integration of mental health activities with those of public health are discussed at three levels: prevention, care, and rehabilitation. It is indicated that the most important treatment used at present is chemotherapy, although electroshock and insulin continue to be used. Great importance is given to occupational and recreational therapy. Psychotherapy is applied in groups and occasionally to individuals. It is reported that at present in Mexico there are 129 institutions specializing in mental health with 8,072 beds, or 1 bed for every 4,336 of the population. Professional training and research activities are briefly mentioned.

Department of Neurology, Mental Health and Rehabilitation
Mexico, D. F.

137 Brownlee, George. The toxicity of new drugs. Pharmaceutical Journal, 1963, 190, 140-141.

In a lecture on drug toxicity, the four stages postulated in the transition from a novel chemical compound to a drug acceptable for human use were demonstration of worthwhile improvement in pharmacological activity, including adequate toxicity tests in laboratory animals, clinical pharmacological investigation; a well-designed comparative clinical trial, and release for general clinical use. Extensive pharmacological testing with no less than two separate animal species should be utilized to test compounds for potential teratogenicity, a procedure which would have obviated the thalidomide tragedy. Repeated doses of the drug may result in drug-induced hypersensitivity manifested as an immediate or delayed anaphylactic reaction, the latter often observed with the barbiturates, sulphonamides, and chlorpromazine. Other toxic reactions include prolonged administration of MAO inhibitors followed by amphetamine or cocaine which precipitates a hypertensive crisis, or potentiation of pethidine by MAO inhibitors which produces acute pethidine poisoning.

King's College
University of London
London, England

138 Hirsh, Herman. The general practitioner and the former mental hospital patient. General Practitioner, 1963, 27, 113-118.

Suggestions for general practitioners in managing former mental hospital patients are presented by a former general practitioner who is now in the private practice of psychiatry and psychoanalysis. Recognizing the ambulatory psychotic is discussed in terms of typical complaints, their manner of presentation, and the denial of symptoms. The need for the practitioner to be familiar with psychotropic agents and their dosage is stressed. Psychologic problems in management of these patients are given as "dos and don'ts" under such headings as 1) respect for the patient, 2) helping the family to adjust, 3) attempting psychotherapy, and 4) identification with the patient. Avoiding the unconscious as expressed in fantasies and dreams is contraindicated for the general practitioner; he should put his emphasis on staying with reality. Signs of relapse of the more obvious types are given. Suggestions are made with respect to answering the questions of both the patients and their families.

(No address)

139 Pitt, Brice & Markowe, Morris. A new pattern in day hospital development.

The West Middlesex Day Hospital. British Journal of Psychiatry, 1963, 109, 29-36.

The development of day departments in general hospitals as part of the day hospital movement in Great Britain is reviewed, to show the shifting emphasis in psychiatric treatment from the mental hospital to the community which it serves. It is concluded that the type of unit described in this report is desirable. The aims in establishing the experimental day hospital were (1) to provide patients who need hospital care with daily contact with family and home and thus have an alternative to inpatient treatment; (2) to curtail patients' hospital stay and provide a stepping stone to future domestic and working life; (3) to make available concentrated outpatient treatment for patients for whom the conventional type is too brief or infrequent. Patients attended 5 days a week. Drugs, electroconvulsive therapy, and some psychotherapy were given. Staff was provided by an associated mental hospital. There were 100 patients whose ages ranged from 18-70 years. The diagnoses were: depressive illness, schizophrenic illness, anxiety state, paranoid state, inadequate or psychopathic personality, hypomania and others. Of the 100 patients, 76 were discharged. Fifty-seven of these were improved; 19 were not improved. Thirty-one were employed shortly after discharge. The intention was that no patient would stay over 3 months, but exceptions were made when it was justifiable. (9 Refs.)

St. Clement's Hospital
London, E.3, England

140 Kraines, S. H. Evaluation of psychotropic drugs in private practice. A symposium. Diseases of the Nervous System, 1963, 24, 181-184.

The most effective psychotropic drug or drug combinations which answer the special demands and urgencies of private practice are discussed. Clinical preference and addicting properties, as well as pitfalls in clinical drug evaluation, are pointed out. The drugs of choice by the five panelists in the average case in private practice were as follows: 1) polysynaptic inhibitors such as meprobamate and chlordiazepoxide for anxiety states, 2) MAO inhibitors and imipramine for endogenous depressions (manic depressive), 3) amitriptyline for involutional melancholias, 4) phenothiazine for manic states, and 5) the same for schizophrenia. The phenothiazine derivatives were also useful in anxiety states and those depressive illnesses which produce agitation and marked tension. Paraldehyde, the barbiturates, glutethimide, ethchlorvynol, and the amphetamines are potentially the most addicting psychotherapeutic drugs. Questions and answers from the question period are added to this report.

Chicago, Illinois

141 Tec, Leon. Durabolin in anorexia nervosa. American Journal of Psychiatry, 1963, 120, 282.

The successful treatment of two severe cases of anorexia nervosa with Durabolin is described. Two girls (14 and 10 yrs. of age) who had shown earlier signs of emotional disturbance, suffered from severe weight loss due to refusal to eat. Their weight dropped to approximately two-thirds of their body weight at the beginning of the episode. Neither psychotherapy nor drug treatment was successful. In both cases two injections, i.m., of Durabolin were administered. Both subjects responded within 1 month with dramatic results. They not only regained the weight they had lost, but increased it within 3 months. Their psychic, as well as physical, health improved.

Mid-Fairfield Child Guidance Clinic
Norwalk, Connecticut

142 Faurbye, Arild, Jacobsen, Ove, Kristjansen, Palle, & Munkvad, IB. Imipramine-N-oxide: preliminary investigation of a new antidepressive drug. American Journal of Psychiatry, 1963, 120, 277-278.

The results of this study indicate that imipramine-N-oxide, a new antidepressant, is valuable in the treatment of endogenous depressions. The clinical effect in some patients appeared to be more rapid than with imipramine and amitriptyline. Imipramine-N-oxide was investigated in an uncontrolled study with 20 female and 8 male patients with typical endogenous depressions. Doses ranged from an initial 30 mg daily to a maximum of 150-200 mg. Several patients responded well to a lower dosage. Full remission was seen in 9 female and 3 male patients in less than 1 week to 5 weeks' treatment. Seven patients clinically improved and eight patients were unchanged during the treatment. Side effects included hypomaniac symptoms and two patients developed toxic delirium of short duration. Insomnia, dryness of mouth, and slight dizziness were also reported. The side effects were fewer and less severe than those presented during treatment with imipramine. (3 Refs.)

Sct. Hans Mental Hospital
Roskilde, Denmark

143 Davis, Richard E., Brauchi, John T., & Greaves, Donald C. Somatic disease or symptom? Somatic complaints as clues to masked psychiatric depressions. Journal of the Kansas Medical Society, 1963, 64, 104-106.

Depression, a common psychiatric illness, is often obscured by somatic complaints or by complaints centered about a prosthetic device. In essence, this is a report of the relationship between ophthalmologic complaints and depressive disease. Three cases are discussed which illustrate a depression masked by or occurring with complaints, about eyeglasses, the purpose being to point out that patients who persistently voice apparently ungrounded complaints about a prosthetic device may be psychiatrically or psychologically depressed. In all cases, after treatment for the depressive illness with imipramine or ECT, the eyeglass complaints subsided.

Dept. of Psychiatry
University of Kansas Medical Center
Kansas City, Kansas

144 Sargant, William. Drugs for depression. British Medical Journal, 1963, 5327, 401-402. (Letter)

The treatment of depression under general hospital conditions is successful with antidepressants. Combinations of dexamphetamine and amylobarbitone appear effective in psychopathic types of depression. Isocarboxazid and phenelzine are useful in treating "atypical" depression. Fifty percent of the patients suffering from endogenous depressio are relieved by imipramine or amitriptyline.

These drugs also help prevent relapses following the use of ECT. The authors have not found any fetal injuries due to hydrazine. They feel that the general practitioner now has an effective treatment for depressed states.

Department of Psychological Medicine
St. Thomas's Hospital
London, S.E.1, England

145 Kline, Nathan S., & Sacks, William. Relief of depression within one day using an M.A.O. inhibitor and intravenous 5-HTP. American Journal of Psychiatry, 1963, 120, 274-275.

Of 50 ambulatory patients with depressions, 39 reacted to DL5-hydroxytryptophane plus MAO inhibitor with a definite or marked effect within 24 hours. The authors' hypothesis was that tryptophane would enhance the effect of MAO inhibitors, since the level of an amino acid or its derivatives could occasion the response delay. Intravenous doses of 5-HTP ranging from 10 to 50 mg, with best results in the 25-50 mg range, were administered to private patients with depressions. The MAO inhibitor used was alpha-methylbenzylhydrazine (Actomol). Two patients received pargyline (Eutonyl), one isocarboxazide (Marplan), and one tranylcypromine. The response to the injection ranged from 12 hours to permanent relief (i.e. for 2 months of followup). Of 20 patients with classical "pure" depression, 18 had a definite or marked effect and 2 failed to respond. Of 30 patients with schizoaffective depressions, 15 had a partial or weak response, 7 had a definite or marked effect, and 8 failed to respond. Side effects including nausea, vomiting, headaches, dryness of mouth, transient hypertension and gastric distention occurred in 12 patients. Divided doses of 5-HTP over a few hours reduced the side effects. (6 Refs.)

Rockland State Hospital
Orangeburg, New York

146 Dorfman, Wilfred. Combined drug treatment. American Journal of Psychiatry, 1963 120, 275-276.

This clinical note reports on the successful treatment of patients with involutional psychosis with a combination of perphenazine (Trilafon) and amitriptyline (Elavil). Additional ECT or psychotherapy aided in decreasing the number of treatments necessary. The patients treated with either drug plus psychotherapy or drug plus ECT were in the following diagnostic groups: involutional psychosis, manic depression, schizoaffective, psychoneurosis, and psychophysiological disorder. The author reports that a review of charts shows that patients who were given varying doses of 1-2-4 mg perphenazine in addition to amitriptyline t.i.d. were improved in less time than those receiving only amitriptyline. In severe cases 25 mg amitriptyline were given and 4 mg perphenazine. Drugs plus psychotherapy were used in 41 patients. Twenty-eight improved, of which 11 had involutional psychosis; of the 13 subjects unimproved only 1 had had that diagnosis. Drugs plus ECT were used on 27 patients. Twenty-five were improved, of which 18 belonged to the involutional psychosis group. Both unimproved patients belonged to that group also. The failures with drugs plus psychotherapy were in the schizoaffective and psychoneurotic groups. (2 Refs.)

1921 Newkirk Ave
Brooklyn, New York

147 Fraser, H.F., Jones, B.E., Rosenberg, D.E., & Thompson, A.K. Effects of addiction to intravenous heroin on patterns of physical activity in man. Clinical Pharmacology and Therapeutics, 1963, 4, 188-196.

The general clinical observations, the behavior and attitude of the patients, and their consistent performance in motor tests indicate that the reduced activity observed during addiction to heroin is not due to physical debility nor to psychomotor impairment but to reduced responsiveness of the patients to ambient stimuli. Physical activity measurements were made during 30 days of placebo administration followed by 60 days of addiction to intravenous heroin.

The daily measures of activity selected were: (a) Hours horizontal in bed, (b) hours of sleep, (c) hours off ward, (d) pedometer miles. The experiments indicate that techniques may be used to measure daily activities which require minimal directed participation of the subject and which do not significantly influence degree and quality of activity. Compared with placebo, heroin increased activity initially but depressed activity when chronically administered over a long interval of time. When patients received heroin chronically, they showed a pronounced tendency to retreat from all forms of activity and social contacts.

National Institute of Mental Health
Addiction Research Center
USPHS Hospital
Lexington, Kentucky

148 Fahy, Peter, Imlah, Norman, & Harrington, John. A controlled comparison of electroconvulsive therapy, imipramine and thiopentone sleep in depression. Journal of Neuropsychiatry, 1963, 4, 310-314.

Sixty patients with depressive syndromes of moderate severity were treated in 3 groups: (1) Electroconvulsive therapy (ECT) with 35 percent good response, (2) imipramine (Tofranil) by injection with 31 percent good response, and (3) biweekly thiopentone sleep treatment with 12 percent good response. Treatment was limited to 3 weeks under constant inpatient observation and weekly progress assessment with doctor interview and staff observations. Group 1 was given ECT with thiopentone and scoline anesthesia (twice a week for 3 weeks), group 2 was given Tofranil (i.m. 50 mg twice daily for 3 weeks), group 3 was given sodium thiopentone (i.v. 5g biweekly for 3 weeks). The only other drugs given were nightly barbiturate hypnotics when needed. The groups were similar in regard to age, sex, diagnosis, prognosis, and history of previous illness. Trial analysis was done on 17 cases ECT, 15 Tofranil, and 17 thiopentone. Side effects such as allergic rash, feeling of general malaise, and acute toxic drug reaction with fever, glandular swellings, hemorrhagic rash, and delirium eliminated three Tofranil patients from the study. Three patients on thiopentone were dropped because of rapidly deepening depression and the necessity for alternative therapy. At final rating, the differences between ECT and Tofranil were not marked, though both seemed superior to thiopentone. (9 Refs.)

Uffculme Clinic
Birmingham 13, England

149 Inglis, J., Jones, R. P., & Sloane, R. B. A psychiatric and psychological study of amitriptyline (Elavil) as an antidepressant. Canadian Medical Association Journal, 1963, 88, 797-802.

Findings suggest that amitriptyline is a useful drug in the treatment of psychoneurotic depression and probably also in the depression of manic-depressive psychosis; present data do not answer the question whether it is superior to electroconvulsive therapy in the latter condition. The antidepressant effects of the drug were investigated by means of psychiatric assessment (objective criteria) and psychological testing (10 measures) of 20 depressed patients who were compared, before and after treatment, with a placebo-treated control group of 14 similar patients. After 3 weeks on doses of 150 mg/day, 13 out of 20 in the experimental group were rated as improved, compared with 3 of the 11 controls ($p < .05$). Clinical improvement was associated with changes on some psychological tests. No persistent adverse side effects were observed. Three stages of assessment of new drugs are discussed. (36 Refs.)

Department of Psychiatry
Queen's University
Kingston, Ontario, Canada

150 Hamelberg, William & Bosomworth, Peter J. Evaluation of ephedrine test. Journal of the American Medical Association, 1963, 183, 782-783.

Clinical findings revealed in this study have shown the ephedrine test to be

unreliable as a screening test in predicting the occurrence of hypotension during anesthesia in patients receiving known or unknown antihypertensive or tranquilizing drugs. The ephedrine test was performed on all surgical patients with a history of receiving antihypertensive or tranquilizing drugs. In addition, 10 patients attending the hospital's hypertensive clinic were tested. There also were 10 normal individuals in whom a determination of the BP and pulse rate response to 5 mg of ephedrine was noted. Hypotension during induction of anesthesia was defined as a 25 percent reduction in systolic BP from control levels. For those patients who had been receiving reserpine and guanethidine sulfate, four became hypotensive during surgery. The ephedrine test predicted hypotension in one of these patients. For those patients on chlorpromazine, two became hypotensive, one of whom was predicted to do so in the ephedrine test. Similar findings were noted with the other patients involved in this study. The study indicated that patients receiving known or unknown antihypertensive or tranquilizing drugs have a significantly higher incidence of hypotension during anesthesia and the ephedrine test cannot be considered reliable as a screening measure for these patients.

Department of Anesthesiology
Ohio State University
Columbus, Ohio

151 Hoagland, Robert J., & McCarty, Richard J. Treatment of drug-induced comma: effectiveness of methylphenidate. American Journal of the Medical Sciences, 1963, 245, 189-197.

Intravenous administration of methylphenidate (Ritalin) accelerated return to consciousness of comatose patients who had taken depressant drugs to commit suicide, and also produced desirable vasopressor effects. A 4-page table presents summaries of 16 cases; more complete case reports are presented on 5 patients. Details of treatment are included and the advantages of prompt restoration of consciousness are summarized. The authors' experiences have shown that methylphenidate can abolish effects of barbiturates, ethyl alcohol, ethinamate, meprobamate, phenothiazines and other depressant drugs. Methylphenidate intravenously administered in doses up to 920 mg/12 hours, produced no undersirable effects. It is suggested that the long prevalent belief that analeptics are valueless in the treatment of coma be discarded.

Department of Medicine
U. S. Army Tripler General Hospital
Honolulu, Hawaii

152 Herman, Emil, & Pleasure, Hyman. Clinical evaluation of thioridazine and chlorpromazine in chronic schizophrenics. Diseases of the Nervous System, 1963, 24, 54-59.

Thioridazine was judged an effective tranquilizer and advantageous in being relatively devoid of extrapyramidal reactions when compared with chlorpromazine. A double-blind clinical evaluation of 80 chronic schizophrenics (average age 46.6 years) was undertaken for the purpose of establishing a therapeutic index for the 2 phenothiazines, as measured by their effect in chronic schizophrenics. Ward behavior and individual symptoms were rated before and after treatment. There was no placebo control. Studies and subsequent clinical use indicate that a daily dose of 600 mg over a period of 18 weeks was adequate to provide a good measure of the relative value of the 2 drugs. Symptoms improved with both drugs, but neither could be rated superior. There was no significant difference between the drugs in regard to ward behavior. A much lower incidence and degree of parkinsonism was found with the use of thioridazine than with chlorpromazine. (16 Refs.)

Middletown State Hospital
Middletown, New York

153 Hunter, H., & Stephenson, G. M. Chlorpromazine and trifluoperazine in the treatment of behavioural abnormalities in the severely subnormal child. British Journal of Psychiatry, 1963, 109, 411-417.

Chlorpromazine and trifluoperazine improved

the behavior patterns of hyperactive, severely subnormal children, male and female, average age 11 years. A 48-item behavior inventory (given in an appendix) was used in a blind crossover study which included 6-week periods on both drugs, a placebo, and a control period of no treatment. Order of administration of the two drugs was counterbalanced. The individual optimum dosage level for trifluoperazine ranged from 3 mg to 24 mg daily, with an average of 11 mg. The dosage level of chlorpromazine varied from 75-750 mg daily, with an average of 291 mg. Side effects included extrapyramidal symptoms, one case with each drug, and two cases of drowsiness and apathy with chlorpromazine; no blood dyscrasias, liver damage or hypotension were observed. Description and discussion of the development of the behavior inventory are included. Results showed that both drugs were significantly effective in the control of hyperactivity and behavioral abnormalities in 18 children, none of whom had a higher Terman-Merrill Scale score than 39 (7 were untestable).

(No address)

154 Hordern, Anthony, & Somerville, Don M. Clinical trials in chronic schizophrenia. Medical Journal of Australia, 1963, 50, 40-43.

A controlled trial confirms clinical impression that combined trifluoperazine and tranylcypromine therapy is effective in treating chronic schizophrenic female patients. The advantages of mental hospital setting for clinical research, as well as difficulties in conducting controlled trials, are enumerated. The problems involve the effect of milieu, faults in methodology, difficulties in assessment and faulty handling of results. As an illustration of ways to circumvent these difficulties, a controlled triple-blind study was conducted with 75 chronic female patients who were assigned to one of three groups. Each group received one treatment for 9 weeks: combined tranylcypromine and trifluoperazine, placebo and trifluoperazine, or two placebos. Clinical assessment of symptoms and behavior using a rating scale based on the VA Multidimensional Scale for Rating Psychiatric Patients was completed by physicians and nurses. The combined treatment was significantly better than the placebo, whereas trifluoperazine alone gave results only slightly better than placebo. Extrapyramidal side effects were treated with Cogentin, and general side effects (headache, nausea, etc.) were treated by dose reduction. (12 Refs.)

Mental Health Research Institute
Melbourne, Australia

155 Abraham, Hilda C., Kanter, Victor B., Rosen, Ismond, & Standen, J. L. A controlled clinical trial of imipramine (Tofranil) with out-patients. British Journal of Psychiatry, 1963, 109, 286-293.

Imipramine in low dosage produced improvement in outpatients suffering from depression; the degree of improvement was not related to the diagnostic categories used. A double-blind trial was designed so that all patients received placebo at different stages and all received the drug, thus no patient remained untreated for an extended period. The 80 cases were diagnosed as reactive, neurotic, endogenous, and unclassified or mixed. The development and prestandardization of an objective measure of depression and recovery from depression of the inventory type is described. The experimental design allowed assessment of placebo effect at different stages of therapy. Problems associated with outpatient experimental trials are discussed, as are side effects and followup findings. The side effects included dry mouth, perspiration, skin reactions, anxious reactions, dizziness, constipation, heachaches, and in a very few cases, falling or fainting. No severe toxic reactions were noted. The majority of the cases needed further treatment for prolonged periods after the trial was completed.

The Camden Clinic
London N.W.1, England

156 Altschule, Mark D., & Brem, Jacob. Periodic psychosis of puberty. American Journal of Psychiatry, 1963, 119, 1176-1178

The findings in patients with periodic pubertal psychosis suggest that in at least some patients the cause of schizophrenic psychosis is metabolic and not sociologic (environmental). The clinical course of an instance of periodic psychosis in puberty is described. The findings in this and similar patients discussed in the literature, indicate the existance of a psychotic syndrome in boys and girls that begins at puberty. The partial similarity to another periodic cyclic syndrome, that which occurs postpartum, is pointed out. The findings, in cases such as the one reported, show the inadequacy of the hypotheses concerning the sociologic etiology of schizophrenia, and also emphasizes that which is called schizophrenia consists of a heterogeneous group of conditions.

Waverley
Worcester, Massachusetts

157 Bordeleau, Jean M., Lazure, Denis, Desrosiers, Max, Douyon, Lamarque, & Morin, Luc. Evaluation of perphenazine in the treatment of Haitian psychotics. Canadian Psychiatric Association Journal, 1963, 8, 111-115.

Psychopharmacological treatment of mental illness as evaluated in the present study, using the drug perphenazine, is the only available and certainly the most practical method of initiating substantial psychiatric management in an underdeveloped country like Haiti. The Centre de Psychiatrie in Haiti admitted 430 patients during its second year of operation; 123 of these were inpatients of whom 28 were readmissions. Pharmacological treatment was used for 80 percent. Therapy was evaluated in 91 patients of whom 81 received perphenazine alone or in combination with other agents. Improvement was graded on a scale of 0 to Grade 3. Grade 2 improvement, indicating disappearance of psychotic and neurotic symptoms, or Grade 3 improvement indicating progress sufficient for resumption of normal activities was noted in 80 percent of the patients who received perphenazine alone and in 58.5 percent of those who received combination therapy. The latter percent is somewhat misleading in that illness in this group was more severe. Extrapyramidal reactions were the major side effects.

Centre de Psychiatrie de Port au Prince
Haiti

158 Brock, Joseph T., & Dyken, Mark. The anticonvulsant activity of chlordiazepoxide and Ro 5-2807. Neurology (Minneapolis), 1963, 13, 59-65.

Chlordiazepoxide (Librium) and Ro 5-2807 (Valium) decreased the frequency and intensity of motor seizures in patients with focal brain damage and epilepsy. The test method used on 32 patient inmates of a state hospital was designed to determine the effectiveness of medications in controlling their motor seizures. A latin-square design was used in which the drugs were given to all the patients. Doses of 10 and 27 mg t.i.d. chlordiazepoxide and 5 and 10 mg t.i.d. Ro 5-2807 were administered. In earlier studies by other investigators, 100 mg of phenobarbital had always proved superior to acceptable doses of other anticonvulsants. In this study which included both the two experimental drugs and the drugs used by the earlier investigators, it was found that Ro 5-2807 and chlordiazepoxide were as effective as phenobarbital. They were also equally well tolerated. Because the test involved only 3 days of treatment, caution is expressed by the authors in regard to the therapeutic value of the anticonvulsant activity of these experimental drugs.

New Castle State Hospital
New Castle, Indiana

159 Brown, D. G., Hullin, R. P., & Roberts, J. M. Fluid distribution and the response of depression to E.C.T. and imipramine. British Journal of Psychiatry, 1963, 109, 395-398.

Twenty-eight patients with primary depressive disorders showed clinical improvement and 22 of the 28 showed an increase of extracellular fluid volume (ECF) during the course of treatment with electroconvulsive therapy or imipramine. In six of the patients, the fluid volume fell, possibly due to the fact that they may belong to a nosologically distinct group. Eighteen patients were treated with ECT and 10 with imipramine. Extracellular fluid volume was assessed using a modified thiocyanate method. Clinical improvement was judged using a clinical rating scale. Small gains in body weight were seen in 20. Findings are discussed in relation to previous work on sodium metabolism and water balance in depressive disorders and it is suggested that a shift of fluid from intracellular to extracellular spaces could be the reason for the increase in ECF in response to imipramine and ECT.

University Dept. of Psychiatry
15 Hyde Terrace
Leeds 2, England

160 Buckman, C., Pinsley, I., & Krell, A. Clinical comments on Indoklon convulsive therapy. Journal of Neuropsychiatry, 1963, 4, 178-181.

Indoklon (hexafluorodiethyl ether) convulsive treatment is simple, safe and effective with the results comparable to electroconvulsive therapy. One hundred forty-four patients were treated with Indoklon, 29 patients by the inhalation procedure and 115 by the intravenous method. The patients, in experiencing partial paralysis and a choking sensation caused by the inhalation method, became apprehensive. The Indoklon vapor escaping from the mask during administration caused personnel present to be uncomfortable. A 5 percent solution of Indoklon given intraveneously and preceded by a muscle relaxant was sufficient to produce the desired seizure. The drug is safe and nontoxic; however, there was an occasional case of a sclerotic vein, with the number of cases increasing when a 10 percent solution was used. In presenting his method for using Indoklon inhalation, Dr. Gunn (who discovered the article) suggests three precautionary measures -- administration of atropine, succinylcholine, and oxygen.

Kings Park State Hospital
Kings Park, New York

161 Burgstiner, Carson B. The use of promazine, meperidine, and scopolamine in labor and delivery. Journal of the Medical Association of Georgia, 1963, 52, 101-103.

Intravenous injection in recommended dosages of a balanced analgesia consisting of promazine, meperidine, and scopolamine results in satisfactory relaxant, amnesic, analgesic and antimetic effects and accords the mother and infant a wide margin of safety in labor and delivery. The effects of a balanced type of analgesia, consisting of promazine, meperidine, and scopolamine were observed during labor and delivery on the obstetric service of Memorial Hospital of Chatham County, Georgia. The ataraxic effect of promazine resulted in fewer doses of narcotics and barbiturates. No significant reduction of uterine contraction was noted, nor was any significant circulatory or respiratory depression noted. The average APGAR score for infants was well within a wide margin of safety. Labor in primigravidae and multiparae was noticeably reduced in duration. All types of delivery were performed without additional medication. The incidence of nasuea and vomiting was quite low.

(No address)

162 Chesrow, Eugene J., Kaplitz, Sherman E., Breme, John T., & Sabatini, Raoul. Acetophenazine (Tindal) in the treatment of 80 chronically ill patients with anxiety and tension: double-blind study. Journal of the American Geriatric Society, 1963, 11, 445-448.

Acetophenazine is an effective agent for relief of anxiety and tension in chronically ill patients. Fourty-four males and 36 females with medical diagnoses of cerebral arteriosclerosis, chronic alcoholism, multiple sclerosis, cerebral palsy, paraplegia, and tabes dorsalis were suffering from anxiety, tension, agitation, nervousness, apprehension, and/or restlessness.

Sixty patients received 10 mg of acetophenazine for 6 months. Blood chemical determinations and urinalyses were normal. Psychological tests revealed better balance in emotional patterns and interpersonal relationships as well as improved memory orientation and concentration in 93 percent of the acetophenazine treated patients. According to clinical observations, excellent or good results were found in 85 percent of the drug group, and in 5 percent of the control group. There were no significant side effects.

Oak Forest Hospital
Oak Forest, Illinois

163 Claridge, G. S., Wawman, R. J., & Davies, M. H. Sedation threshold, autonomic lability and the excitation-inhibition theory of personality. I. The cold pressor test. British Journal of Psychiatry, 1963, 109, 548-552.

A suggested relationship between barbiturate tolerance and the responsiveness of the autonomic nervous system is reported. The blood pressure response to cold water was examined in 32 mixed neurotic and 13 normal control subjects on whom measures of sedation threshold and Archimedes spiral aftereffect were also obtained. The spiral aftereffect correlated significantly and positively with the pre-stress blood pressure level, which, in turn, showed a near zero correlation with sedation threshold. The results are suggested as supporting the view that it is necessary to hypothesize two sources of arousal to account for some of the postulates of Eysenck's theory of personality.

Dept. of Experimental and Clinical Psychology
Barrow Hospital
Barrow Gurney, near Briston, England

164 Joglekar, G. V., Balwani, J. H., & Mutalik, G. S. Evaluation of antipruritic drugs in normal volunteers. Clinical Pharmacology and Therapeutics, 1963, 4, 197-199.

Ergotamine has no antipruritic effect and further trials are needed to confirm similar claims for trimeprazine (Temaril). The antipruritic effect of trimeprazine and ergotamine was evaluated in medical students by use of the double-blind technique. Itching was induced by Mucuna pruriens (Cowage) ointment. Ergotamine tartrate was found to be ineffective, whereas no definite opinion could be formed regarding trimeprazine tartrate.

Department of Pharmacology and Medicine
Bijramjee Jeejeebhoy Medical College and
Sassoon Hospitals
Poona, India

165 Karliner, William. Clinical experiences with intravenous Indoklon: a new convulsant drug. Journal of Neuropsychiatry, 1963, 4, 184-187.

Results with intravenous Indoklon (hexafluorodiethyl ether) equal those of inhalation Indoklon and both are superior to electroshock. Ten percent solution of Indoklon is more practical than a 5 percent solution for intravenous use because of the smaller amounts needed and the rapidity with which it is exhaled. Simplicity of equipment with amounts that can be accurately measured make the intravenous method preferable. Fewer secondary or multiple convulsions are observed with the intravenous procedure, although the therapeutic results of both methods are the same. Booster therapy of Indoklon was recommended for those patients who tend to have recurrences of their illness. The article is discussed by Dr. Thigpen who agrees with the author and outlines his procedure of using Evipal (hexobarbital) succinylcholine, and positive pressure oxygen at the time of Indoklon therapy, and suggests caution in giving electroconvulsive treatment to patients on tranquilizers.

West Hill Sanitarium
Riverdale, Bronx, New York

166 Karp, Eric, & Pollack, Max. Comparative studies of chlorpromazine and imipramine. III. Critical flicker fusion thresholds in psychiatric patients. Psychopharmacologia,

1963, 4, 452-458.

Chronic administration of chlorpromazine showed a statistically significant decrement in CFF threshold when compared with placebo or imipramine; imipramine showed a nonsignificant decline in CFF as compared with placebo. A group of cooperative, voluntarily hospitalized psychiatric patients was investigated in a double-blind fixed-dosage, placebo-controlled study. When retested after 5 weeks while receiving 1,200 mg/day of chlorpromazine (with 1.2% procyclidine added) or 300 mg/day of imipramine, the chlorpromazine group showed a mean decrement significantly greater than that for imipramine (p=.01). The differences in mean change between the imipramine and placebo groups were not statistically significant. Both drugs increased group variance as compared with placebo. This variability was significantly related to age. Mention is made of other factors which might account for increased variability in response to the drugs.

Dept. of Pediatrics,
Albert Einstein College of Medicine
New York 61, New York

167 Krantz, John C., Jr. Volatile anesthetics and Indoklon. Journal of Neuropsychiatry, 1963, 4, 157-161.

Indoklon (hexafluorodiethyl ether) produced electroshock type of seizures with no harmful aftereffects and is a good therapy tool in psychiatry. Several anesthetic agents and their efficacy are discussed including Vinamar, Vinethene, Fluroromar, and Fluothane. Indoklon was found to produce seizures resembling electroshock therapy, without harmful sequelae, when inhaled by a variety of animals. It was useful in diagnosing subclinical epileptogenic foci. While pentobarbital sodium, thiopental sodium, ether, and Fluoromar blocked convulsive action of Indoklon, mephenesin, and dilantin sodium did not. Thidione increased Indoklon resistance. No toxic effects were noted. Indoklon was effective with four mentally ill patients in producing electroshocklike seizures through inhalation followed by uneventful recovery and no clouding of memory. Solution of 5 percent Indoklon, 76 percent Carbowax 300, 19 percent water injected into jugular vein of animals unvariably produced seizure and the results were produced when the solution was injected into the cephalic vein. Indoklon injection in man was compatible with atropine sulfate, thiopental sodium and succinyl-choline chloride.

Dept. of Pharmacology
University of Maryland
Baltimore, Maryland

168 Krakowski, A. J. Long-term study of a new psychotropic drug in private psychiatric practice. Psychosomatics, 1963, 4, 44-51.

An analysis on the effects of a new psychotropic drug -- diazepam -- reveals its usefulness in a wider spectrum of activity than its parent compound chlordiazepoxide (Librium). Diazepam was found not only to be effective in the anxiety states but surprisingly effective in both neurotic and psychotic depressions and in obsessive compulsive personality disorders, two groups notably resistant to treatment. A series of 124 private psychiatric patients was treated with diazepam (Valium) for 1 week to 10 months. The clinical results were excellent or good in 97 patients (78.2%). Fifty-two patients showing anxiety reactions alone or with depressive, and/or phobic features obtained complete or substantial remission in 86.5 percent; 25 obsessive compulsive patients in 68 percent and 11 with personality disorders in 81.8 percent. Of the 15 psychotic patients, 10 had good or excellent response. Dosage varied from 5 to 160 mg/day, with the average daily intake ranging from 14 mg in reactive depressions to 32.5 in the psychotic group. From further studies, it appeared that dosages of over 20 mg/day result in a high incidence of side effects, the more prominant being drowsiness, ataxia and fatigue. A battery of laboratory tests done before and during chemotherapy has shown no toxic effects on metabolism, liver, kidneys, or hemopoietic organs. This drug was found to be particularly useful in facilitating psychotherapy in patients who previously had difficulty in verbalizing.

Physicians and Champlain Valley Hospitals
Plattsburgh, New York

169 Badham, J. N., Bardon, L. M., Reeves, P. O., & Young, A. M. A trial of thioridazine in mental deficiency. British Journal of Psychiatry, 1963, 109, 408-410.

Thioridazine is reported as effective in controlling behavior disorders in severely subnormal patients. An uncontrolled clinical study was conducted with two groups of mentally deficient male and female patients including children. Group A as characterized as grossly disturbed and as not having responded to earlier drug treatment; group B is described as disturbed but adequately controlled by drugs such as chlorpromazine. Group B included 30 epileptics who received anticonvulsants during the test. Of the 58 patients in group A, 44 were judged improved by thioridazine, 13 markedly. In group B, 59 of the 85 patients were improved including 31 of the 46 previously on chlorpromazine. The effective dosage for adults was of the order of 100 mg t.d.s. while it varied in children between 25 mg b.d. and 100 mg q.d.s. Results with children are cited as especially promising. Only 21 of 143 patients showed side effects. In the children, there were no side effects.

Harperbury Hospital
St. Albans, England

170 Crisp, A. H. Differentiation of two genetically specific types of depression by the response to antidepressants. Lancet, 1963, 7276, 326-327. (Letter)

A study by Pare et al (1962) which purportedly substantiates a hypothesized biochemical basis for depression is severely criticized. Only 22 patients were utilized to assess the effects of Parnate and Parstelin (tranylcypromine and trifluoperazine) in recurrent depression. Inadequate data appear to have been derived from a multiplicity of sources, and patient response is inconsistent at best. Several patients manifested drug-induced improvement during the first illness, but failed to respond during the recurrent illness. On the basis of such discrepancies, these drugs fail to exert any great direct biochemical effect on the mechanism underlying depression, or differentiate metabolically between types of depression. Placebo responses appear important, as do responses between patient and close relatives who may have been influenced by knowledge of the response elicited from respective relatives.

Academic Psychiatric Unit
Middlesex Hospital
London, W.C.1, Great Britain

171 Friedman, Arnold P. Studies in the pharmacotherapy of headache. Neurology, 1963, 2, 27-33.

Methysergide (3 mg b.i.d.) or placebo was administered to 224 refractory patients with frequent migraine headaches (classic, ordinary, and cluster headaches) over a period of 30 months as a prophylactic or preventive measure. Methysergide alone produced improvement (50 % reduction in headaches) in 79 percent of the 98 patients with common migraine. Of 55 common migraine sufferers treated with both methysergide and placebo, 47 improved with methysergide and 9 with placebo, a fact that was statistically significant. An improvement of 77 percent was noted in patients with classical migraine. In 40 patients with cluster headache treated with methysergide alone and 10 treated with drug and placebo, 90 percent of the patients showed improvement. Of the responsive patients, approximately 30 percent suffered from moderate nausea, dizziness, epigastric distress, etc. Drug discontinuation was necessitated in two patients due to loss of pulse and cyanosis in the legs. An additional group of 156 patients was treated less than 2 months. Methysergide brought about an improvement in 68. Side effects occurred in 87, and 56 had to discontinue therapy. Various investigators have determined the efficacy of chlordiazepoxide, meprobamate, hydroxyphenamate, reserpine, and chlorpromazine in ameliorating migraine headaches. The drug of choice for obtaining symptomatic relief is still ergotamine tartrate. Many techniques, including determination of blood levels of drugs, bioassays, radioactive tracers, and electronic devices permit patients subjective responses to be validated by objective parameters.

(No address)

172 Fryer, D. G., & Timberlake, W. H. A trial of imipramine (Tofranil) in depressed patients with chronic physical disease. Journal of Chronic Diseases, 1963, 16, 173-178.

Thirty-one patients with organic disease who had high scores on the depression scale of the MMPI were randomized and treated with either imipramine (100 mg/day) or placebo in a double-blind study. The MMPI was re-administered at the end of 4 weeks to measure change. In 14 patients, the alternative drug was administered subsequently so that each acted as his own control. No significant change in the depression score resulted from the use of imipramine as compared with placebo. A slight reduction in the hypochondriacal overemphasis on physical symptoms was recorded.

Department of Neurology,
Lemuel Shattuck Hospital
Jamaica Plain, Massachusetts

173 Fox, Vernelle. Carpenazine in the withdrawal phase of acute alcoholism. Journal of the Medical Association of Georgia, 1963, 52, 167-170.

Carphenazine compared favorably with previously used compounds such as chlorpromazine, promazine, triflupromazine and other phenothiazine derivatives in the treatment of the acute alcoholics. Carphenazine was the principal medication employed with 96 patients (79 men and 17 women) mean age 45. All were suffering acute aftereffects of an extended period of drinking. Dose of 20-25 mg every 2-4 hours. Oral dosage of 12.5 or 25 mg (4-6 times a day) was used for starting and maintaining 39 patients. In all except a few patients, other medications were also employed, notably 8 doses of 100 mg hydroxyzine hydrochloride administered to 64. Evaluative criteria were established and are reported. Withdrawal symptoms cleared within 3 days in 55 percent of the patients. These 55 percent represent 76 percent of those who initially received i.m. carphenazine; a day or two more was required for the remaining 45 percent. Side reactions were nearly nonexistent though special mention is made of the painful nature of the intramuscular injection.

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Atlanta, Georgia

174 Heninger, G., & DiMascio, A. Psychopharmacology of imipramine and desimipramine. Federation Proceedings, 1963, 22, 627. (Abstract)

Desimipramine has been shown to be one of the primary metabolites of imipramine, an agent used in psychiatry as an antidepressant agent. Preliminary clinical trials have shown that desimipramine also has antidepressant properties. This study was intended as a parametric investigation of the effects of these two agents when administered to normal male subjects. The study was done double-blind and with a placebo control. The two drugs were tested at 50, 100, and 200 mg doses. Drug actions were recorded pre-drug, and 2, 4, and 8 hours after the oral administration of one of the doses of the drugs, on a battery of tests that included physiologic psychomotor, cognitive functioning, and affect state measurements. Desimipramine produced only minor tachycardia. In contrast, imipramine produced marked hypnotic effects as evidenced by a slowing or impairment of almost all functions examined and, in a subjective feeling of diminution of mental and physical energy. The procedure allowed for comparison of the magnitude of drug effects the dose-response curves, and potency. On the basis of the comparison of drug actions, conclusions are drawn relative to their chemical structure-behavioral effect relationships, as well as to their implications for usage in clinical psychiatry.

Mass. Mental Health Center
Boston, Massachusetts

175 Journal of Kansas Medical Society. Journal of Kansas Medical Society, 1963, 64, 16, 17, 22.

A young deaf and dumb woman with a chronic paranoid personality disorder manifested a psychotic illness 9 months after the birth

of her third child. She received isocarboxazid (10 mg t.i.d.) and chlordiazepoxide (10 mg t.i.d.) for more than 6 weeks, after which her condition improved considerably. Discontinuation of medication at one point immediately precipitated a relapse into psychotic behavior, which was laboriously alleviated. Constant collaboration between the general practitioner and psychiatrist coupled with medication and familial understanding have contributed to maintaining a marginally adequate social adjustment. Her physical handicap greatly complicated communication with the psychiatrist. Maintenance therapy, both medicinal and psychotherapeutic, was required to maintain stability.

(No address)

176 Krueger, H. J. Symposium on psychoendocrinology. VII. ACTH--therapy for the epileptic men. Canadian Psychiatric Association Journal, 1963, 8, 49-50.

Six male epileptic patients suffering from convulsions resistant to common anticonvulsant therapy were treated with hydantoin (dosage unspecified) and 20-40 units a day of ACTH for 3-6 weeks; then deoxycorticosterone and vitamin C were administered. Good results were obtained in three patients, two of whom were freed from convulsive seizures. In one patient, however, the frequency of seizures increased. In another case the EEG became nearly normal. Ketosteroid and total corticoid excretion remained unchanged.

Pfalzische Nervenklinik, Landeck,
Landau/Pfalz, Landeck, Austria

177 Lappolla, Anthony. Tranylcypromine and chlorpromazine in hospitalized female patients. General Practice, 1963, 26, 6, 7, 9.

During a 6-month period, 104 female patients 16 acute schizophrenia, 33 chronic schizophrenia, 6 manic depressive, 14 involutional psychosis, 26 CBS, 2 psychosis with syphilitic meningoencephalitis and 7 psychoneurotics), ages 13 to 74, who had been hospitalized for 30 days to 14 years received tranylcypromine (10 mg 1, 2, or 3 times a day) combined with chlorpromazine (25-200 mg/day) for 2-6 months. According to weekly evaluations, excellent responses to therapy occurred in 44 patients, good responses in 29 patients and poor responses in 31 patients. Initial signs of improvement usually were noticeable within the first week of treatment. Combination therapy was most effective in chronic schizophrenics, those with psychoneurotic or involutional depression, and patients in the depressed phase of a manic-depressive psychosis. Treatment was least successful in patients with chronic brain syndrome complicated by convulsive disorders. Side effects included insomnia, decreased systolic blood pressure, transient dizziness, weakness, and tiredness.

Camarillo State Hospital
Camarillo, California

178 Lees, F., & Burke, C. W. Tranylcypromine. Lancet, 1963, 7271, 13-16.

Tranylcypromine (10 mg b.i.d.) was administered to 60 outpatients, ages 26-59, with depression, tension, or anxiety often in addition to organic disease, for 10 days to 8 months. Impressive amelioration occurred in 2-3 days in 45 patients, with relief of depression, apprehension, agitation, insomnia, weeping, etc. Fifteen patients failed to improve. Severe side effects including tachycardia, throbbing headache, dyspnea, postural hypotension, and vomiting occurred in 11 patients. Slight side effects such as wakefulness, mild neck stiffness, and tiredness were observed in four patients. No correlation was detected between duration of treatment and nature or severity of side effect. Several other informative studies are cited, and 11 representative case histories offer further elucidation.

Department of Neurology
St. Bartholomew's Hospital
London, E.C.1, Great Britain

179 Le Gassicke, John. Tranylcypromine. Lancet, 1963, 7275, 270. (Letter)

A 23-year-old depressed man took phenelzine,

etryptamine, and nialamide /dosages unspecified/ before he took tranylcypromine (up to 200 mg/day p.o.) for 9 months. While under the influence of tranylcypromine, he made tentative attempts toward resocialization and even sought employment. Difficulty in obtaining a continual supply of tranylcypromine precipitated a return to his previous behavioral patterns. As tranylcypromine is structurally similar to amphetamine, analogous energizing effects are partially responsible for symptomatic improvement in depressive illness.

Jordanburn Hospital
Edinburgh, Great Britain

180 Mall, G. Symposium on psychoendocrinology. VI. Some contributions to the psychoendocrinology of premenopausal oestrogen deficiency. Canadian Psychiatric Association Journal, 1963, 8, 46-48.

Fifty women (31 endocrine psychosyndrome, 5 psychoneurosis, 7 hebephrenia, 4 endogenous depression, and 3 postmenstrual phasic psychosis), 25 being of the leptosomic constitutional type, were given hormonal substitution treatment with ethinyoestradiol (dosage unspecified). Subjective disorders, chiefly anxiety, seemed to prevail in the mental picture; personality, drive, and cerebration were considerably affected, especially the rate of mental association. In addition, serious imbalances of autonomic function existed. Therapy cured or at least alleviated these mental and autonomic symptoms.

Clinic for Nervous Diseases, Landeck,
Landau/Pfalz, Landeck, Austria

181 Leitch, A., & Seager, C. P. A trial of four anti-depressant drugs. Psychopharmacologia, 1963, 4, 72-77.

Imipramine was found to be more effective than pheniprazine, now withdrawn because of hepato-toxicity, but not significantly different from phenelzine and phacetoperane in treating hospitalized patients with depressions. A 4-week double-flind study with weekly ratings of 13 symptoms is described. The 96 inpatients suffering depression not sufficiently severe to warrant ECT were randomized to the 4 drug treatments. The ratings were made on a 5-point scale from "Worse" to "Recovered." No drug was as effective as earlier reports have indicated; this finding is discussed. Side effects such as tremulousness, giddiness, blurring of vision and abdominal distension were reported. All side effects were connected with phacetoperane. Forty-five percent of the patients became well enough for discharge, while with imipramine it was better at 60%. A discussion of opposing views as to the best way of assessing drugs is included. (7 Refs.)

Barrow Hospital
Garrow Gurney, near Bristol, England

182 Lingjaerde, Odd. Clinical experiences with thioproperazine ("Majeptil") in chronic schizophrenia, psychotic excitation, and senile agitation. Psychopharmacologia, 1963, 4, 281-293.

Thioproperazine, a phenothiazine derivative, is a very rapidly acting and effective drug in manic and maniclike states as well as in severe senile or presenile agitation. In chronic schizophrenia, former good results of discontinuous treatment reported by other investigators could not be confirmed in two courses of treatment. Thioproperazine chemically resembles prochlorperazine with the chlorine atom replaced by a dimethylsulphamoyl group. It possesses greater antiemetic properties and cataleptic activity than prochlorperazine but has a weaker effect on the autonomic system. Sedative properties are low. Since it has marked cataleptic properties pharmacologically, it produces many neurological symptoms in patients. It also produces numerous clinical and psychological syndromes. Of 17 chronic intractable schizophrenic women (10 hebephrenics, 2 catatonics, 1 paranoid, 3 undifferentiated, 1 doubtful categ[illegible]) who received thioproperazine by discontinuous treatment, 5 improved and only 2 had a lasting effect. Such side effects as dyskinesia, nausea, dryness of mouth, and vertigo were occasionally reported. Five manic patients and five with atypical

maniclike attacks received the drug intramuscularly. All but one showed marked improvement within 1-7 days. Side effects were few but increased later on oral dosage after the first week of treatment. Four severely deteriorated patients suffering from senile or presenile states of agitation which had proved resistant to several ataractic drugs showed improvement from the first day. Intravenous injection of 7.5 mg of thioproperazine had a rapid sedative effect in one patient. There was no change in pulse rate or blood pressure. Promazine alone had been quite ineffective even in higher dosages. (20 Refs.)

Lier Mental Hospital
Lierbyen, Norway

183 McGovern, John P., Haywood, Theodore J., Thomas, Orville C., & Fernandez, Anthony A. Studies with a benzodiazepine derivative in various allergic diseases. Psychosomatics, 1963, 4, 203-206.

Diazepam (Valium) appeared effective in reducing the tension-fatigue syndrome, and somatic symptoms in patients who had chronic allergic diseases with significant emotional overlay. An uncontrolled clinical evaluation of diazepam in a series of 423 private patients, ages 1-75 with allergic rhinitis and/or other allergic disease was carried out. Reduction of tensions and of somatic symptoms such as cough, wheeze, rash, and itching was obtained in 92 percent of the patients after medication lasting from 1 week to 7 months with good to excellent results in 76 percent. Compared with earlier experiences with chlordiazepoxide, diazepam appeared to exert a more favorable effect on certain types of patients with allergic disease and emotional overlay. No serious side effects developed during the study. (10 Refs.)

Dept. of Allergy
University of Texas Postgraduate School of Medicine
Houston, Texas

184 Maire, Frederick W., & LaVeck, Gerald D. Evaluation of nialamide as an adjunct in the treatment of seizure disorders. Diseases of the Nervous System, 1963, 24, 38-45.

Results indicate that nialamide reduced significantly the incidence of seizures in 48 mentally retarded epileptic patients with organic brain damage. Seizures were completely controlled in 2 patients only. Nialamide (1-[2-(Benzylcarbamyl) ethyl] -2-isonicotinoyl-hydrazine), an MAO inhibitor was given as an adjunct to other seizure medications such as phenobarbital or Gemonil, Dilantin, and Mesantoin. Daily dosage in those patients who had only light or no side effects was 25 mg t.i.d., gradually decreasing over 2-3 weeks, until its discontinuation after 10 months. There was an increase in seizures in 11 of the patients. Nialamide was continued under close supervision. The drug appears nontoxic, but laboratory tests, including evaluation of hepatic function, should be maintained during treatment. Of the 35 patients who benefited, a majority were severe epileptic cases, whereas those with increased seizure incidence were from a group having two or less convulsions per month. This may point to possible cerebral mechanisms involved in the effect of nialamide on seizure phenomena.

Mental Health Research Institute
Fort Steilacoom, Washington

185 Marks, V., & Shackcloth, P. Tranquilizers and pregnancy tests. British Medical Journal, 1963, 5348, 52-53.

Immunological tests described in this investigation are so sensitive to an increased chorionic gonadotrophin excretion that their use as pregnancy tests is not disturbed by the administration of tranquilizers. In light of recent investigations reporting false-positive pregnancy tests in women receiving tranquilizers, a study is described revealing the specificity of immunological tests as an effective test for pregnancy regardless of whether tranquilizers have been administered to the test patient. Comparison with a well-known test for pregnancy, the Hogben bioassay technique, is described. Correct positive results were found to be

obtained much earlier with the immunological tests than with the Hogben test where false negatives are common in early pregnancy. In up to 2 days following a therapeutic abortion, immunological pregnancy tests may remain positive though the Hogben test rapidly reverts to normal. The immunological tests used in these investigations appear to be more sensitive; and in the case of phenothiazine-treated subjects, a more specific indication of increased chorionic gonadotrophin excretion than the Hogben bioassay technique and because of this sensitivity, it is unnecessary to withhold tranquilizer therapy prior to undertaking these pregnancy tests. (7 Refs.)

Area Laboratory at West Park Hospital
Epsom and Group Laboratory
Epsom District, Epsom, Surrey, England

186 Millar, John. A trial of fluphenazine in schizophrenia. British Journal of Psychiatry, 1963, 109, 428-432.

The substitution of fluphenazine in 38 chronic female schizophrenics who were being treated with chlorpromazine resulted in a statistically significant improvement in the behavior of the patients based on scores on a prescribed behavior rating scale as well as nurses' reports and frequent clinical observations. Fluphenazine appears to be about 40 times as potent weight for weight as chlorpromazine and its action is sustained so that most patients can be treated satisfactorily with a single daily dose. Thirteen of the 38 chronic female schizophrenics involved in this study developed parkinsonian symptoms which represented the only side effects of fluphenazine. These side effects were usually slight, affected only the hands and were not disabling. The symptoms were controlled with benzhexol hydrochloride given in doses of 2-4 mg t.i.d. Fourteen of the patients had developed parkinsonism while receiving chlorpromazine. Of these only four developed tremor while receiving fluphenazine. Results of the study also indicated that chlorpromazine was more effective than a placebo but less effective than fluphenazine in producing greater improvement in the 38 schizophrenic females. This clinical impression was supported by psychiatric and behavior ratings as well as nurses' notes and frequent clinical observations.

Carlton Hayes Hospital
Narborough, near Leicester, England

187 Murphree, H. B., Sugerman, A. A., Jenney, E. H., & Schultz, R. E. Quantitative EEG effects in male chronic schizophrenics of phenothiazines and deanol. Federation Proceedings, 1963, 22, 510. (Abstract)

Quantitative analysis shows a difference between EEG's of normals and those of male chronic schizophrenics. Objectives of the present study were to determine whether significant alterations in the EEG's of schizophrenics as measured by this technique are produced by antipsychotic drugs, whether the EEG changes, if any, are in a direction toward normal, and whether any concomitant behavioral changes occur. Chlorpromazine was chosen as a sedative phenothiazine, perphenazine as a nonsedative phenothiazine, and deanol as a long-acting stimulant. After baseline recordings, 16 subjects were given daily divided doses according to double-blind procedure as follows: deanol 1 g (4 weeks), chlorpromazine 300 mg (4 weeks), blank (10 weeks), perphenazine 32 mg (4 weeks), perphenazine 32 mg+ deanol 1g (4 weeks). All except blank produced significant EEG changes toward normal. Chlorpromazine effects lasted at least 10 weeks in some cases.

Pharmacology Section, Bureau of Research in Neurology and Psychiatry
New Jersey Neurologic & Psychiatric Institute
Princeton, New Jersey

188 Onuaguluchi, G. Assessment of drug therapy in parkinsonism. British Medical Journal, 1963, 5328, 443-448.

Orphenadrine (100 mg t.i.d.), methylbenztropine (4 mg t.i.d.), or placebo was administered for 3 weeks in a double-blind study to 2 groups of patients, ages 42-62, all with postencephalitic Parkinson's disease. Most

of the patients were already receiving benzhexol. Before the trial was begun, all were placed on 15 mg of benzhexol daily and gradually reduced to 5 mg daily. Weekly evaluation included measurement of grip strength with dynamometer, amount of active and passive flexion and extension of the neck, ability to write, ability to swallow, frequency of oculogyric crises, etc. An "acute" study performed on eight patients with severe tremor involved random administration of orphenadrine (100 mg), benzhexol (10 mg), methylbenztropine (4 mg), or placebo. The 3-week study resulted in satisfactory improvement in 15 patients who received orphenadrine, but improvement was seen in only 5 patients treated with methylbenztropine. No improvement was observed with placebo. Depression was alleviated in 15 patients by orphenadrine. Side effects of orphenadrine included difficulty with micturition, myoclonus, dizziness, nervousness, a hemorrhagic tendency, and a burning sensation in the throat. No side effects occurred with methylbenztropine. In the "acute" experiment, optimal drug activity ensued within 2 hours after orphenadrine administration, and 2-3 hours after benzhexol. The period of maximal activity was difficult to ascertain for methylbenztropine.

Department of Materia Medica and Therapeutics
University of Glasgow
Glasgow, Great Britain

189 Overall, J. E., Hollister, L. E., Honigfeld, G., Kimbell, I. H., Jr., Meyer, F., Bennett J. L., & Caffey, E., Jr. Comparison of acetophenazine with perphenazine in schizophrenics: demonstration of differential effects based on computer-derived diagnostic models. Clinical Pharmacology and Therapeutics, 1963, 4, 200-208.

By statistical analysis, acetophenazine was more effective with "paranoid" patients than perphenazine, which was more effective with "core schizophrenic" types. Acetophenazine was compared with perphenazine under controlled conditions in 98 schizophrenic men who were new admissions. Inpatient Multidimensional Psychiatric Scale and the Brief Psychiatric Rating Scale were used for clinical evaluation. There was improvement of most factors on both rating scales from either treatment, with no difference between the drugs on mean score changes. There was a marked difference between the drugs in the spread of the mean score changes, acetophenazine varying more than perphenazine. To determine if specificity of patient type influences reactions to the drugs, patients were classified as paranoid or core schizophrenic by computer analysis of the initial ratings on the BPRS. The study was not impaired by the mild reactions or complications of the treatment. Perphenazine induced more extrapyramidal disturbances than acetophenazine. Abnormal laboratory findings were relatively frequent before treatment and occurred sporadically during treatment. Their significance depends on accompanying clinical findings.

Department of Psychology
Kansas State University
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190 Bellville, Titus P., Heistad, Gordon T., & Schiele, Burtrum C. A comparative study of thioridazine and carphenazine using sequential analysis. Psychopharmacologia, 1963, 4, 53-65.

The clinical effectiveness of a new phenothiazine drug, carphenazine, was compared with one in widespread use, thioridazine. The differences were slight. Carphenazine had a lower incidence of side effects such as hypotension and gastrointestinal complaints. The statistical method used was sequential analysis. Drugs were administered on a double-blind basis. When one member of a matched pair showed improvement or worsening, results were compared, evaluated for that particular pair and the study terminated for them. At the end of the sequential analysis (6 weeks) based on global clinical ratings, it could be stated with a high degree of confidence that both drugs were preferred in at least 25 percent of all the authors' patients and that neither drug was preferred in 75 percent of similar patients. In sequential analysis, qualitative differences cannot be identified, but nonsequential

methods showed carphenazine to be more favorable in respect to side effects. (8 Refs.)

University of Minnesota Hospitals
Minneapolis 14, Minnesota

191 MacMaster, Duncan R., & Alamin, Khosrow. Treatment of severe weight loss with methandrostenolone-a less virilizing anabolic agent. American Journal of Psychiatry, 1963, 120, 179-180.

The anabolic agent, methandrostenolone, when given at an average dose of 5 mg b.i.d., will produce weight gain in mentally disturbed patients with severe weight loss. It has a low incidence of side effects and produces a feeling of well being and improved psychological attitude. Forty-seven female patients ranging in age from 15 to 86 years were treated for an average of 45.55 days with 17 alpha-methyl, 17 beta-hydroxyandrosta-1,4-dien-3-one or methandrostenolone (Dianobol). It has proven to be the most potent anabolic steroid tested, having 10 times the activity of methyltestosterone. All patients showed an increase in weight for a group average of 7.81 pounds or 37.61 percent during the 29-60 day treatment. Side effects were acne, hirsutism, and in one case menorrgagia. Three cases developed amenorrheia and reduced menses were reported in five cases. No changes in blood pressure or pulse were noted.

New Jersey State Hospital
Greystone Park, New Jersey

192 Challas, George, & Brauer, William. Tourette's disease: relief of symptoms with R1625. American Journal of Psychiatry, 1963, 120, 283-284.

The palliative effect of R1625 (Haloperidol) is described in two case histories of boys, ages 16 and 9 with Tourette's disease. The symptoms displayed by the subjects were multiple tics accompanied by coprolalia. Various medications, psychotherapy, and in one case hypnosis had failed to produce a lasting effect. Case I was given a dose of R1625 1.5 mg t.i.d. for 9 weeks. Improvement was achieved immediately. Abnormal liver function occasioned discontinuance of the drug. Case II was given R1625 0.5 mg t.i.d. Within a week, the symptoms subsided and did not return in a 3-month followup period. Initial complaints of sleepiness, blurred vision, and motor restlessness ceased. (8 Refs.)

State University of Iowa
Iowa City, Iowa

193 Padula, Louis J., & Karliner, William Inhalation Indoklon convulsive therapy. Journal of Neuropsychiatry, 1963, 4, 182-183.

Beneficial results from the use of inhalation Indoklon convulsive therapy were obtained in 89 out of 92 psychotic (schizophrenic) patients at West Hill Sanitarium, Bronx, New York. The present study reports the effects of inhalation Indoklon convulsive therapy on 92 psychotic patients at West Hill Sanitarium. Eight-nine of these patients were schizophrenics and three of them were suffering from a depressive episode of the manic-depressive type. Of the 89 schizophrenic patients, 16 were much improved after inhalation Indoklon convulsive therapy, 70 were improved, and 3 remained unimproved. The three manic-depressive patients were all much improved. The advantage in using Indoklon is that the patient accepts treatment much more readily when told he will not receive ECT. At no time was the prolonged posttreatment apnea noted with ECT encountered. A few patients had an excessive posttreatment excitement period which was controlled by 3-3/4 or 7½ grains of sodium amytal intravenously. The simple procedure for administering this convulsive agent is described. The production of the seizure is usually very smooth and offers no complications. However, the authors do point out that the presence of upper respiratory disease contraindicates use of this agent. These experiences reveal that Indoklon inhalant can be safely administered by all psychiatrists and should be a very valuable addition to the armamentarium of the psychiatrist in the treatment of his psychotic patients.

West Hill Sanatarium
Riverdale, Bronx, New York

194 Patel, Natoo, Mock, David C., Jr., & Hagans, James A. Comparison of benzphetamine, phenmetrazine, d-amphetamine, and placebo. Clinical Pharmacology and Therapeutics, 1963, 4, 330-333.

Benzphetamine (50 mg/tablet), phenmetrazine (25 mg/tablet), d-amphetamine (5 mg/tablet), and placebo were given for 12 weeks to volunteer subjects wishing to lose weight. All three amphetamines were associated with highly significant weight loss compared to placebo. Thirty-two hospital employee volunteers with excess weight of from 3-86 pounds were matched into groups on the basis of excess weight. A 4 week control period without medication was followed by a fixed regimen of 1 tablet before each of 3 meals, without formal dietary restrictions. Dunnett's t-test comparing multiple treatment groups to a control showed that there was no significant difference between the three amphetamines. The reduction of caloric intake showed no significant statistical difference in any of the groups. Appetite suppression was the same for all. The amphetamines had a more sustained anorexic effect than the placebo. None of the agents caused clinically important changes in blood pressure, pulse, or respiration rates. Insomnia, dryness of mouth, and indigestion were side effects of all active agents, the latter two in a lesser degree in the placebo group. Benzphetamine caused sleeping problems for the entire study duration, while sleep improvement was noted in the placebo group. Some of these getting the three active agents showed mood elevation.

University of Oklahoma School of Medicine
and Veterans Administration Hospital
Oklahoma City, Oklahoma

195 Peterman, Albert F. Evaluation of methysergide maleate. For the interval treatment of vascular headache. Mind, 1963, 1, 91-94.

A total of 51 patients, ages 19-81, with chronic recurrent vascular headaches received methysergide (2 mg q.i.d., p.o.) for 1 day to 24 months. Patients were examined every 2 weeks. Excellent results were obtained in 26 patients (51%), 22 with histaminic cephalalgia, 2 with migraine headache, and 2 with mixed tension-vascular headache. Poor results were obtained in 20 patients (39%), and fair results were obtained in 5 patients (10%). In 22 of the 32 patients with histaminic cephalalgia, methysergide was effective in relieving the cluster of acute unilateral headaches within 24 hours. In 8 patients with migraine headache, 2 manifested excellent results, 1 fair, and 5 poor. Of the 20 who responded poorly, 15 had concomitant serious tension and/or depression syndromes. The following side effects occurred in 17 patients (33%): nausea in 8 patients (necessitating drug withdrawal in 5), 4 paresthesias, 2 leg cramps, 2 dizziness, and 1 blurred vision with a feeling of intoxication. Side effects diminished if medication was continued for more than 3 days.

Palo Alto Medical Clinic
Palo Alto, California

196 Rawlings, W. J., Ferguson, Russell, & Maddison, T. G. Phenmetrazine and trifluoperazine. Medical Journal of Australia, 1963, 10, 370. (Letter)

Trifluoperazine [dosage unspecified] was administered to pregnant women with a propensity toward habitual abortion, and out of 341 pregnancies, 80 abortions, 11 perinatal deaths, and 5 congenital malformations ensued. The incidence of congenital abnormalities in this series (1.46%) approximated that of the incidence occurring in the total population (1.5%), a fact which precludes the existence of potential teratogenicity in trifluoperazine. Erroneous reports implicating trifluoperazine as a cause of deleterious fetal anomalies have generated completely unfounded anxiety in many communities.

Royal Women's Hospital
720 Swanston Street
Carlton, Victoria, Australia

197 Roy, Paul B., Mercure, Justin, Lebel, George, & Bourque, Robert. Contribution a l'etude de "Librium" dans le traitement des alcoholiques. (Contribution to the

study of Librium in the treatment of alcoholics.) Union Medicale du Canada, 1963, 92, 218-220.

Chlordiazepoxide given to 50 hospitalized alcoholics relieved anxiety and tension. It did not cause habituation. The patients treated had an average age of 37.8. The doses in general were 25-50 p.o. 4 times per day. Intravenous injection was administered only to those patients showing severe agitation and a clinical picture of delirium tremens accompanied by hallucinations. Even at high doses neither hypotension nor respiratory disturbances were observed. Besides its muscle relaxing properties, chlordiazepoxide caused increase of appetite and weight gain. Side effects such as ataxia, enuresis, and pollakiuria disappeared by decreasing the dosage. It was observed that chlordiazepoxide may have a potentiating action on alcohol.

Domremy-Montreal, Inc.
Montreal, Quebec, Canada

198 Sainz, Anthony. Benzquinamide: a preliminary report. American Journal of Psychiatry, 1963, 119, 777-778.

Benzquinamide (average therapeutic dose 100-400 mg q.i.d. for 2 weeks-6 months; average miminal maintenance dose 25-150 mg q.i.d.; effective dose 25-150 mg q.i.d. and maximal useful dose 300-1,200 mg q.i.d.) was administered to 51 patients (7 manic-depressive, manic; 12 hyperkinetic schizophrenics; 8 diffuse organic brain syndromes with severe agitation; 5 anxiety states; 14 simple stress reactions with severe agitation; and 5 with endogenous depression), while 16 received placebo according to a triple-blind technique. Of the seven manic depressives, four experienced full remission, and one chronic case showed substantial improvement. Of the hyperkinetic schizophrenics, six showed reduction in overactivity, without alteration in underlying psychosis. Two patients with organic brain syndrome showed relief from agitation, while the remainder were unresponsive aside from three who were slightly overstimulated. Drowsiness occurred in anxiety neurotics 15-30 minutes after drug ingestion. Complete relief from agitation and apprehension was observed in 13 out of 14 patients with simple stress reactions. No effect was observed with endogenous depressions. Side effects constituted two cases of drowsiness and one case of gastritis. Extensive laboratory tests failed to manifest variations from normal ranges. Benzquinamide is a superior tranquilizer definitely indicated for simple stress reactions. It has no antipsychotic or antidepressant activity, and no angolytic properties.

Division of Research
Marcy State Hospital
Marcy, New York

199 Scanlan, Eileen P. & May, Arthur E. A controlled trial of Taractan in chronic schizophrenia. British Journal of Psychiatry, 1963, 109, 418-421.

Slight improvement was judged on the basis of clinical assessment when chlorprothixene (Taractan) was employed in chronic schizophrenia. A double-blind crossover study is reported in which placebo was compared with the active drug. No significant differences between placebo and chlorprothixene were discovered using an 85-item psychotic behavior profile, EEG, and pathological laboratory tests on blood, urine, and liver function. When final ratings of a clinical assessment scale were grouped as improved, no change, and worse, the difference between treatments was significant $p=<.01$. On the average, patients gained weight while on the drug and lost weight on placebo.

Rainhill Hospital
Liverpool, England

200 Scott, J. C. Phenistix in psychiatric practice. Scottish Medical Journal, 1963, 8, 30-33.

Phenistix was found to be reliable in detecting chlorpromazine in urine. A survey of 600 mental hospital patients using the Phenistix (paper-reagent strip) test on morning specimens of urine was conducted. In addition to reliable detection of chlorpromazine, the test revealed patients who were not taking prescribed chlorpromazine as

well as those excreting aspirin metabolites. Data on duration of excretion of chlorpromazine are presented and discussed. Relatively uncontrolled survey results of 87-88 percent detection led to a controlled study of 100 male patients' urine specimens. Detection in this study was 100 percent. Earlier and lower detection rates are explained on the basis of methodological differences. Test conditions necessary to achieve results comparable to those of this study are described. It is suggested that Phenistix may have a place in general practice and hospital outpatient clinics in detecting those failing to take prescribed chlorpromazine as well as in detecting unofficial consumption of aspirin.

Royal Mental Hospital
Dundee, Scotland

201 Seleny, F. L. & Spoerel, W. E. Observations on postoperative vomiting. Canadian Anaesthetists' Society Journal, 1963, 10, 30-36.

Prochlorperazine (intramuscular) proved more effective than trimethobenzamide on postoperative vomiting patients. Postoperative patients (123) who vomited twice following recovery from anesthesia were treated with trimethobenzamide (66), prochlorperazine (40), and dimenhydrenate or cyclizine (9). Eight received no treatment. Treatment was effective with 39 percent after trimethobenzamide injection within a 6-hour period after injection, and with 63 percent after prochlorperazine injections. Duration of operation, preoperative medication, position of patient, and type of anesthesia (cyclopropane, fluothane, nitrous oxide plus i.v. agent, ether, penthrane or regional anesthesia) had no significant influence on the degree of vomiting. About 50 percent of the patients did not vomit after receiving treatment. Whenever first injection with antiemetic drug was not effective, subsequent treatment with the same drug or other antiemetics was disappointing. Though prochlorperazine appeared superior to trimethobenzamide in recurrent vomiting, both drugs had little effect. A higher dosage of trimethobenzamide given intravenously is considered for further investigation.

U. of Western Ontario
Victoria Hospital
London, Ontario

202 Seltzer, Albert P. Trifluprom azine as an adjunct in preanesthetic treatment prior to rhinoplasty. Journal of the South Carolina Medical Association, 1963, 59, 166-168.

Trifluprom azine appears to be a useful adjunct for the attainment of complete relaxation in rhinoplasty performed under local anesthesia. A study of 200 consecutive rhinoplasty patients, 100 male, 100 female, was conducted. Preoperative medication included amobarbital, 3 gr, morphine sulfate, 1/6 gr, and trifluprom azine (Vesprin), 8 mg to 15 mg depending on age, weight, and route of administration. Complete relaxation is reported in all 200 cases. The usual signs of pain stress were not seen and every patient could be easily aroused and followed instructions during operation. Desirable drugs for combination with trifluprom azine are discussed.

Dept. of Otolaryngology
Graduate School of Medicine
University of Pennsylvania
Philadelphia, Pennsylvania

203 Skarbek, Andrew. Trial of amitriptyline in chronic depression. Diseases of the Nervous System, 1963, 24, 115-119.

Amitriptyline is judged of value in the treatment of chronic depression. A double-blind crossover trial was carried out with 23 female depressive patients with previous negative response to drug therapy. Amitriptyline and placebo were given alternately for 4 periods of 4 weeks' duration. Patients response was judged by changes in clinical state using a 4-point scale. Results with the drug were statistically superior to those with placebo. Side effects were few, mild, and transient with the exception of hypomania in one patient.

Cane Hill Hospital
Coulsdon, Surrey, England

204 Smith, Colin M. Controlled observations on the single case. Canadian Medical Association Journal, 1963, 88, 410-412.

Results of a narcolepsy patient self-rating scale for a single case demonstrated that adrenaline methyl ether was significantly less effective in relieving symptoms than dextroamphetamine or methamphetamine. A trial of the three analeptics in the treatment of a narcoleptic patient using a self-rating scale is described. The scale used in a counterbalanced double-blind paradigm is given in an appendix and provides symptom and complaint scores. With symptom scores, an analysis of variance showed the difference between drugs to be significant at the .05 level. Complaint scores were not statistically analyzed. Pitfalls in use of single case studies are discussed. (6 Refs.)

University Hospital
Saskaton, Saskatchewan, Canada

205 Bender, Lauretta, Faretra, Gloria, & Cobrinik, Leonard. LSD and UML treatment of hospitalized disturbed children. In: Wortis, Joseph (Editor), Recent Advances in Biological Psychiatry, Vol. 5, New York, Plenum Press, 1963, pp 84-92.

Studies with autistic and verbal hospitalized children indicate that LSD and UML intensify awareness and responsiveness in these patients. The children, who were patients on a Children's Research Unit, were selected for the study and evaluated by psychiatrists, psychologists, and ward personnel. Biochemical studies were conducted concomitantly. LSD (25 µg) was given intramuscularly, then orally. It was increased to 150 µg daily; UML was increased from 4 mg to 12 mg daily. About one-half of the group received LSD and one-half UML. The children, diagnosed as having childhood schizophrenia, were in two major categories: half were autistic, regressed, and nonverbal; others were psychotic but verbal and alert. Results in the autistic group showed increased awareness and no serious side effects. In the verbal group, two major changes were observed: 1) a decrease in personalized ideation with gain in accuracy of response, and 2) an inhibition of strongly emotional reactions to cards. A leveling off of response was noticed after several weeks but no conclusions could be reached as to this being a tolerance effect. Biochemical investigations show that LSD and UML increase RBC inorganic phosphate levels and the uptake of serotonin-C^{14} was increased for 2 weeks, then decreased.

Creedmoor State Hospital
New York, New York

206 Warshaw, L. J. & Bennett, H. J. Evaluation of drugs in industry. Archives of Environmental Health, 1963, 6, 227-234.

A comparison of the effectiveness of chlordiazepoxide (Librium), clidinium bromide, the combination of both (Librax), and a placebo in relieving symptoms of gastrointestinal upset, reveal no statistical advantage of the active agents over the inert agent. A method was developed for comparing the effectiveness of drugs in the treatment of acute functional disorder, suitable for clinical pharmacology investigation in the industrial medical department. The method comprised (1) the use of rigid arbitrary criteria for suitable case selection, (2) comparison of the drug with more or less effective preparations and a placebo, (3) employment of a randomized block design for the assignment of subjects to different treatment groups, (4) use of double-blind technique, and (5) observation of number of doses and amount of time required for desired effect, frequency of symptom recurrence after initial improvement, and individual symptom response independent of patient's overall response. The three drugs were highly effective in symptom relief when evaluated 24 hours after onset of treatment. No statistically significant advantage over placebo was displayed. This indicates the tendency to spontaneous improvement of the disorder rather than drug effect. One or two doses of 5 mg chlordiazepoxide (oral) brought substantial symptom relief within 8 hours to more than 50 percent of patients who responded to treatment. Recurrence of symptoms occurred only one-fourth as frequently as after placebo. Chlordiazepoxide

seems to be a useful drug in acute gastro-intestinal upset. In combination with clidinium bromide, chlordiazepoxide did not alter response. Clidinium alone was no more effective than the placebo.

1501 Broadway
New York 36, New York

207 Wawman, R.J., Claridge, G. S , & Davies, M H. Sedation threshold, autonomic lability and the excitation-inhibition theory of personality. II. The mecholyl test. British Journal of Psychiatry, 1963, 109, 553-557.

Further supporting evidence for the view that barbiturate tolerance is related to the level of sympathetic reactivity is presented. A simplified version of the mecholyl (Funkenstein) test was used to investigate autonomic imbalance in 27 mixed neurotic and 7 normal control subjects. Additionally, measures of sedation threshold and Archimedes spiral aftereffect were obtained. Correlation between measures were generally less clear cut than in the previous experiment using the cold pressor test. The complex nature of the cardiovascular response to mecholyl makes quantification difficult. Despite this, the results are viewed as hypothesis supportive.

The Queen Alexandra Military Hospital
Millbank, London, S.W.1, England

208 Dubois, John R., Jr. Neurologic complications of phenothiazine therapy. Henry Ford Hospital Medical Bulletin, 1963, 11, 59-63.

Phenothiazines, which have helped decrease the population of State and Federal mental institutions, have many neurological side effects which are unusual and bizarre. Among these are dystonia ("pseudotetanus"), grand mal convulsion, Parkinsonlike syndrome, akathisia, and catatonia. Moderate withdrawal symptoms have been observed. This study reviews the neurological complications that have been observed since the introduction of chlorpromazine (Thorazine) in the U. S. since 1953. It was the first phenothiazine drug used as a tranquilizer. Various neurological side effects are reviewed in this paper. Dystonia appeared in 90 percent of the reported cases within the first 4½ days after the drug was started. Signs have persisted up to 48 hours after drug discontinuation. Grand mal convulsion may be the only manifestation of a phenothiazine idiosyncrasy. The EEG shows a typical tracing of a seizure pattern. The Parkinsonlike syndrome is the most commonly seen neurological side effect. It is seen in 90 percent of the patients within the first 72 days of therapy. Antiparkinsonian drugs are given. When these are discontinued, the Parkinson signs will only recur in about 20 percent of the patients, though high doses of phenothiazine are maintained. Akathisia is a paradoxical effect of this therapy. It increases the anxiety of the patient. Again 90 percent of the patients developed it within the first 73 days of therapy. Catatoniclike states mimic schizophrenia. These symptoms disappear after withdrawal of the drug. (20 Refs.)

Henry Ford Hospital
Detroit, Michigan

209 British Medical Journal. More hazards of drugs in pregnancy. British Medical Journal, 1963, 5324, 138.

Support for avoiding medications with sedatives, tranquilizers, and hypnotics during pregnancy and for remembering the possibility of early pregnancy in any women of childbearing age is revealed in this survey. Critical consideration is given to a recent report from workers at the Lafayette Clinic and Wayne State University in Detroit stating that the administration of certain tranquilizers, notably meprobamate, to pregnant rats impairs the intelligence of the offspring. The mechanism of the impairment remains unknown but might be due to interference with the physical states of the mothers or to altered development of the fetal cerebral cortex. The results of these experiments may or may not apply to man and they may apply not only to meprobamate but to other tranquilizers not tested. This study brings into clearer focus the difficult task clinicians have in trying to weigh their immediate therapeutic problems against the evidence about the safety of drugs.

(No address)

210 Cohen, Sidney, & Ditman, Keith S. Prolonged adverse reactions to lysergic acid diethylamide. Archives of General Psychiatry, 1963, 8, 475-480.

When properly employed LSD is a relatively safe and important research tool. The actual incidence of serious complications following LSD administration is not known. In reviewing specific complications, certain patterns seem to emerge. The patients who have difficulty with LSD tend to be emotionally labile, often hysterical or paranoid personalities. They are also hypersuggestibl and become overwhelmed with a deluge of anxiety- and guilt-laden insights. Therapists who administer hallucinogenics should clearly recognize their patients' motivations and the potential hazards of a profound consciou ness-changing experience. Sociopathic behavior can on occasion follow the administration of LSD. Until the indications,

techniques, and precautions are better understood, LSD therapy should be restricted to investigators in institutions where close observation of the patient is feasible and appropriate countermeasures are available in case of adverse reactions. It appears that antisocial groups have embraced LSD in addition to the narcotics, amphetamines, and barbiturates and a black market is being created in this country wherein tablets, ampules, and sugar cubes saturated with LSD have become available in the large cities and on some college campuses.

Veterans Administration Hospital
Los Angeles, California

211 Dolenz, Bernard J., & Sprehe, Daniel J. Observations with Indoklon. Journal of Neuropsychiatry, 1963, 4, 190-193.

Indoklon used to induce seizures when compared to ECT, has more advantages, but may cause an occasional thrombosis and renal insufficiency. Fifteen patients, candidates for convulsive therapy, were treated at random with Indoklon and ECT and the two therapies were compared. Pretreatment workup and indications were the same, as were contraindications except for possible renal insufficiency with Indoklon due to Carbowax 300. Indoklon had less postictal confusion, less fear, greater safety, and no toxic effects. While ECT produced immediate unconsciousness, evoked response was simple, and could be used in combined treatment, it requires a complex apparatus and carries a social stigma. Indoklon is more expensive, requires greater skill, causes occasional thrombosis and nausea, and needs a ventilated treatment room to protect personnel. Possible complications of memory, plus those of the musculoskeletal, cardiovascular, and respiratory systems are the same in both. With ECT, convulsions are more sudden, less intense, and of shorter duration than those with Indoklon.

East Louisiana State Hospital
Jackson, Louisiana

212 Lees, F., & Burke, C. W. Tranylcypromine. Lancet, 1963, 7275, 269-270. (Letter)

As McCormick and Blackwell (1963) questioned the validity of a study without controls, it was suggested that they publish their observations with tranylcypromine administered to a homogenous group of depressed patients, with controls. The untoward effects elicited by tranylcypromine are due to its MAO-inhibiting activity. Tranylcypromine should be modified so that it exerts antidepressant action without precipitating the systemic effects accruing from MAO inhibition.

St. Bartholomew's Hospital
London, E.C. 1, Great Britain.

213 Cromie, B. W. Meprobamate. British Medical Journal, 1963, 5355, 502-503.

The author refers to a previous drug series where meprobamate was reported as having caused agranulocytosis. He stressed that according to experience apparently this was an isolated case. In the 6 years since a patient was found to have aplastic anemia some weeks after being treated with meprobamate, "tons of the drug" have been administered without a single similar case. It is suggested that though it is valuable to report every toxic incidence, a sense of perspective should be kept. The author considers meprobamate one of the least toxic agents. (8 Refs.)

John Wyeth & Brother, Ltd.
Taplow, Maidenhead, Berks., England

214 Martin, W. R., Wikler, A., Eades, C. G., & Pescor, F. T. Tolerance to and physical dependence on morphine in rats. Psychopharmacologia, 1963, 4, 247-260.

The effects of large doses of morphine sulfate in nontolerant and tolerant rats as well as the effects of abrupt withdrawal in rats experimentally addicted to morphine are presented and discussed from a psychophysiological point of view. This experimental

study was undertaken to obtain essential information on the characteristics of chronic morphine intoxication and abstinence in the rat and to obtain a quantitative determination of the time course of abstinence associated with abrupt withdrawal. The experimental and observational protocol is included. Measures taken include body weight, temperature, metabolic rate, water consumption, and various forms of motor activity and behavior. Generalizations based on the study and previous work are presented with respect to effects on physiological responses in tolerant and nontolerant rats. The abstinence syndrome of rats is described and is presented as having two phases, the second of which is seen as quite similar to the protracted abstinence syndrome of man. It is suggested that it, therefore, may serve as a model for the study of the basic pathophysiological abnormalities of a process known to occur in abstinent human addicts.

National Institute of Mental Health
Addiction Research Center
Public Health Service Hospital
Lexington, Kentucky

215 Medecine et Hygiene. Les effets secondaires de la thioproperazine. (Thioproperazine side effects.). Medecine et Hygiene, 1963, 578, 32. (Editorial)

Akinesia, lethargy, parkinsonism, rigidity, clonus, choreiform movements, and catalepsy are reported as side effects of thioproperazine (Denham & Carrick, 1961). Aunesley & Maut (1962) report a fatality following a 7.5 mg i.m. injection. Respiratory depression, cardiovascular collapse, agitation and oculogyric crisis have also been reported. The dangers inherent in the drug seem to outweigh its therapeutic benefits.

Rue Michell-du-Crest
Geneva, Switzerland

216 Medecine et Hygiene. Un malheureux effet dans une maladie justiciable d'une auto-administration de chlordiazepoxyde. (An unfortunate effect in a patient due to self-administration of chlordiazepoxide.) Medecine et Hygiene, 1963, 578. (Editorial)

Chlordiazepoxide, taken by a 37-year-old man, is said to be the cause of a car accident due to drowsiness after taking 20 mg of the drug following a midday meal. The patient whose case is reported in the Medical Journal of Australia, 1962, had been prescribed 10 mg chlordiazepoxide t.i.d. for nervous tension and anxiety. He was permitted to take up to 20 mg in the evening, when possible side effects would not endanger him. The author recommends that this drug should never initially be prescribed in a dose above 10 mg t.i.d.

Rue Michell-du-Crest
Geneva, Switzerland

217 Lewis, Ronald G. Chlorpromazine sensitivity simulating the acute abdomen. Medical Journal of Australia, 1963, 10, 371. (Letter)

A 26-year-old woman ingested chlorpromazine (dosage unspecified) on 3 separate occasions and immediately experienced abdominal symptoms severe enough to mimic "acute abdomen." Severe burning, radiating pain, heartburn, dark urine, nausea, and vomiting ensued shortly after drug administration. After the third incident, chlorpromazine was determined to be the causative factor. All liver function tests yielded normal results, aside from an elevation in the SGPT. Although jaundice was not evident, bile was present in the urine during these attacks.

195 Macquarie Street
Sydney, Australia

218 Macdonald, Roderick. Tranylcypromine. Lancet, 1963, 7275, 269. (Letter)

Of 600 inpatients and outpatients treated with tranylcypromine (dosage unspecified) in a British sanatorium, only 14 cases

were reported to have developed severe occipital headaches as a side effect. This side effect occurred only in outpatients and in three cases it was known that methylamphetamine i.v. injections were given concurrently with the drug. The author suggests that limited experience and lack of knowledge of side effects should not be exaggerated to the extent of virtually condemning a drug. Judgment on advantages and side effects of a new drug should be properly balanced.

(No address)

219 McGaugh, J. L., de Baran, L., & Longo, V. G. Electroencephalographic and behavioral analysis of drug effects on an instrumental reward discrimination in rabbits. Psychopharmacologia, 1963, 4, 126-138.

This paper reports an experimental investigation of the effect of psychotropic drugs on the performance of an instrumental reward discrimination and on the cerebral electrical activity of rabbits. Four adult rabbits with implanted electrodes were first trained to pull a ring at the sound of a buzzer for a food reward. They were later trained to discriminate between a continuous (rewarded) and an intermittent (unrewarded) buzzer. No differences were observed in EEG responses to these two stimuli; the EEG was at all times desynchronized. The effect of drugs on responses and EEG was then studied. The drugs investigated tended to fall into three groups: 1) Amphetamine which blocked the discrimination without affecting the instrumental response, the EEG being continuously desynchronized. 2) Chlorpromazine and scopolamine, which blocked concomitantly the discrimination and the instrumental response; during the block the EEG was synchronized. (Eserine, .05 mg/kg, administered during the peak effect of scopolamine, produced an immediate recovery of the discriminative response and a concomitant EEG activation.) 3) LSD, which most effectively blocked the discrimination and instrumental response without showing signs of EEG synchronization. In comparing the results to earlier work, it is suggested that the sensitivity of behavioral tests to drug effects depends on the complexity of the problem and perhaps that EEG sensitivity also depends on problem complexity. With respect to chlorpromazine, it is pointed out that previous work has demonstrated that this drug interferes with the ability of subjects to avoid a noxious stimulus without affecting other abilities. Also the present findings indicate that chlorpromazine may affect complex performance based on approach motivation. (13 Refs.)

Department of Psychology
University of Oregon
Eugene, Oregon

220 Brimblecombe, R. W. Effects of psychotropic drugs on open-field behavior in rats. Psychopharmacologia, 1963, 4, 139-147.

This paper reports experimental results using psychotropic drugs in relation to the use of an open-field test as a screening procedure. Wistar rats were studied in Hall's open-field test 1½ or 3 hours after various doses of 10 psychotomimetic drugs. After eight of these, changes in behavior at the lowest effective dose used included significant decreases in emotional defecati This effect was also found with harmine, at a higher dose but with diethyltryptamine it did not occur at any dose level though a trend was observed. Tests on animals in th familiar environment of their own cages showed that the decrease in defecation was not due to direct effects of the drugs on the alimentary tract. Three stimulant and five depressant drugs were tested but no consistent pattern of activity emerged. Th only drug which caused decrease in emotiona defecation, thiopropazate, also caused concurrent decrease in all other measured categories of behavior. Though all the drugs used, known to have activity in man, did produce behavioral changes in the open field, the doses at which the changes occurred were always higher than effective human doses. The lowest doses of all drug causing changes were 1½ to 20 times higher than human doses except with LSD-25 where the ratio was 1:250-500 and reserpine wher

it was 1:100. These ratio differences are seen as limiting the value of the open field as a screening procedure. In discussing the five drugs, it is pointed out that a decrease in emotional defecation after drug treatment, if unaccompanied by reduction in other behaviors, indicates that the drug may be psychotomimetic and warrants further investigation. With respect to drugs tested other than the psychotomimetics, it is suggested that other tests have greater relevance, though the open-field test may have a place in ranking orders of potency. (13 Refs.)

Chemical Defense Experimental Establishment
Porton Down, Salisbury, Wilts, England

221 Holmberg, Gunnar, & William-Olsson, Ulla. The effect of benzquinamide, in comparison with chlordiazepoxide and placebo, on performance in some psychological tests. Psychopharmacologia, 1963, 4, 402-417.

In a direct comparison between the two active drugs the outcome was in favor of chlordiazepoxide on all significant points. In a double-blind experiment, 20 young, healthy women were given single oral doses of benzquinamide (Quantril) 200 mg, chlordiazepoxide (Librium) 60 mg, and placebo. Before ingestion and 1 and 2 hours after, a battery of psychological tests was applied. Subjective experiences were obtained and are reported. When placebo changes were subtracted from changes obtained with the drugs, both were found to exert a depressant effect on flicker fusion frequency with the action of chlordiazepoxide lasting longer. This drug is of long duration pharmacologically and accumulation of the drug may increase its effects with time. Results are given and discussed for the following tests: auditory span, coordinator tests (two-hand), cancellation test, mental arithmetic, standing steadiness. Subjects ranked the three preparations as to disagreeable effect. Benzquinamide stood out as clearly more disagreeable in its action than either chlordiazepoxide or placebo. Hitherto unpublished data, including chemical structure and dosage, are presented for benzquinamide.

Klubbvagen 7
Danderyd, Sweden

222 Latz, Arje. The differential effects of chlorpromazine and secobarbital on sustained attention in chronic schizophrenics. Federation Proceedings, 1963, 22, 509. (Abstract)

In normal adults, chlorpromazine given in single doses caused greater impairment on sustained attention than did comparable doses of barbiturates. In order to extend these findings to other populations, the author studied the performance of 8 male chronic schizophrenics on tests of sustained attention, response latency, psychomotor output, and cognition after the administration of a placebo and single doses of 100 and 200 mg of chlorpromazine or secobarbital. Positive reinforcement served as an additional independent variable. Reinforcement significantly improved performance on all dependent variables and there was no interaction between drug treatment and reinforcement. Both higher drug doses significantly impaired performance, the effect of chlorpromazine being greater than that of secobarbital only on sustained attention. These findings confirm earlier reports that compared to the effects of a barbiturate, the effects of chlorpromazine are more selective on sustained attention, and in addition the results indicate that the impairment in performance caused by these drugs can be partially modified by the use of reinforcement.

Boston University Medical Center
Boston, Massachusetts

223 Scriabine, Alexander, Weissman, Albert, Finger, Kenneth, Delahunt, Charles S., Constantine, Jay W., & Schneider,

Jurg A. Benzquinamide. A new anxiety drug. Journal of the American Medical Association, 1963, 184, 276-279.

Benzquinamide has been found to induce a specific calming effect in anxious, tense, psychoneurotic adults and adolescents without impairing mental alertness. Support is presented for the usefulness of benzquinamide as a psychotherapeutic agent. Benzquinamide was shown to specifically disrupt conditioned avoidance in rats. Fighting behavior in mice was inhibited by the agent at dose levels at which no muscle relaxation or interference with muscular coordination was observed. The drug was found to simulate potent phenothiazine tranquilizers by blocking apomorphine-induced emesis in dogs. The toxicological evaluation of benzquinamide in various species indicated relative safety of the compound. Described are clinical studies which demonstrate that benzquinamide can reduce anxiety in the psychoneurotic patient without impairing mental alertness. In psychotic patients, benzquinamide was valuable as adjunctive treatment in the relief of anxiety and facilitated accessibility and psychotherapeutic management. (11 Refs.)

Department of Pharmacology
Medical Research Laboratory
Charles Pfizer & Co., Inc.

224 Scheckel, Carl L. Interaction of antidepressants with amphetamine, cocaine, alpha-methyl-metatyrosine, and tetrabenazine. Federation Proceedings, 1963, 22, 627. (Abstract)

Imipraminelike antidepressants were compared with a variety of other compounds using rats conditioned to respond in a continuous avoidance procedure (RS 40", SS 20"). The minimal effective doses that increased rate of avoidance responding (stimulation) were determined for each compound in three tests: 1) amphetamine potentiation, 2) cocaine potentiation, and 3) stimulation in combination with an inactive dose (0.2 mg/kg s.c.) of tetrabenazine (TBZ). Desmethylimipramine, desmethylamitriptyline, amitriptyline, and imipramine (in decreasing order of potency measured in the TBZ-stimulation test) were active in all three tests. Atropine, scopolamine, trihexphenidyl, promethazine, and iproniazid potentiated amphetamine and cocaine, but did not stimulate with TBZ. Chlorpromazine, promazine, azacyclonol, methylphenidate and phenidamine were inactive in all three tests. The imipramine-induced stimulation of amphetamine, cocaine, and TBZ was blocked by 16 hours of pretreatment with alpha-MMT which in addition attenuated, but did not block atropine potentiation of amphetamine. Since alpha-MMT selectively depletes brain levarterenol, the absence of imipramine-induced stimulation in the alpha-MMT pretreated rat indicated that brain levarterenol is involved in the activity of imipramine.

Hoffmann-La Roche, Inc.
Nutley, New Jersey

225 Voronina, M. L., & Tushmalova, N. A. Vliyaniye 5-gidroksitriptofana (predshestvennika serotonina) na pishchedobyvatel'nyye uslovnyye refleksy u krolikov. (Effect of 5-hydroxytryptophane (serotonin precursor) on food-procuring conditioned reflexes in rabbits.) Zhurnal Vysshey Nervnoy Deyatel'nosti imeni I. P. Pavlova, 1963, 13, 1071-1076.

5-hydroxytryptophane (serotonin precursor) inhibited food-procuring conditioned reflexes in rabbits by increasing the latent period of the conditioned reflex and decreasing the number of intersignal reactions. Food-procuring conditioned reflexes were elicited in rabbits using an electric light bulb as the unconditioned stimulus. Five rabbits were given 0.01-5 mg/kg of 5-hydroxytryptophane (5-HTP) intravenously one to two times a week. In addition, three rabbits were administered different doses of 5-HTP once or twice. Altogether 45 experiments were carrried out. In all experiments, food-procuring conditioned reflexes were inhibited by 5-HTP; the extent of inhibition depended on dosage. In two rabbits inhibition was less extensive than in others. The inhibiting effect of 5-HTP was expressed by an increased latent

period of the conditioned reflex and a decreased number of intersignal reactions. The effect appeared sooner with smaller doses and was intensified as doses were decreased. In only one rabbit was the number of intersignal reactions increased. The extent of inhibition of conditioned reflex activity in rabbits varied and, probably, depended on individual characteristics of the nervous system of the animals.

Chair of Physiology of Higher Nervous Activity of the Moscow State University im. M. V. Lomonosov, Moscow, USSR

226 Shchelkunov, Ye. I. Usiliniye tofranilom i khloratsizinom antirezerpinovogo deystviya fenamina v opytakh na krysakh s uslovnymi refleksami. (Potentiation of the antireserpine effect of phenamine with Tofranil and chloracizine in experiments with conditioned reflexes in rats.) Activitas Nervosa Superior, 1963, 5, 4-12.

Tofranil and chloracizine potentiated the antireserpine effect of phenamine in experiments with conditioned reflexes in rats and also prolonged the period of phenamine restoration of conditioned reflexes impaired by reserpine. The antidepressant effect of Tofranil and chloracizine was compared on seven male white rats according to an alimentary conditioned reflex in a maze. The rats received no food and water for 24 hours before the experiment. Two hours after 2 mg/kg of reserpine, administered i.p., a catatonic depression developed with hypertonia, mild tremor of extremities, ptosis, miosis, and diarrhea. Depression lasted about 24 hours and was followed by a restoration of conditioned reflexes. In control experiments 3 hours after administration of reserpine, 1 mg/kg of phenamine was administered i.p. The animals' behavior changed several minutes after administration of phenamine. Conditioned reflexes were studied 15 minutes after the first dose of reserpine and every 15 minutes thereafter. The period of duration of "arousal effect" of phenamine was determined in 5 experiments for each animal. When 5 mg/kg of Tofranil was administered i.p. together with 2 mg/kg of reserpine, the average restoration period of conditioned reflex with phenamine increased more than 5 times as compared with a previous control experiment and it increased almost twice as compared with a subsequent control experiment. Water was used instead of the drugs in these control experiments. Because of similar central effects of Tofranil and chloracizine, the latter was suggested for clinical use as an antidepressant.

Laboratory of Psychopharmacology of the Psychoneurological Institute im. V M. Bekhtereva, Leningrad, USSR

227 Vazquez, A. J. Strychnine-sensitive mechanism in cat rage. Federation Proceedings, 1963, 22, 514.

Strychnine (0.1 mg/kg i.p., less than half convulsive dose) and eserine (0.5 mg/kg i.p.), neither of which produces rage reactions in cats unless administered in lethal dosage, caused rage when administered together. Picrotoxin plus eserine did not. Eserine reduced to 25% the dose of LSD required to induce rage (1 mg/kg i.p.). Paradoxically, strychnine decreased arecoline-induced rage. Previously our group found that LSD and muscarinic, but not nicotinic, agents or eserine produce rage. Eccles has classified strychnine as a blocker of an unknown mediator of postsynaptic inhibition. Except for the strychnine-arecoline antagonism, the present results would suggest that the pathway for LSD-induced rage contains muscarinic cholinergic neurones which are normally subject to direct neural inhibition. However, the arecoline-strychnine antagonism suggests that the mechanism is not so simple. Although LSD-like hallucinatory behavior is also caused by eserine-strychnine combination, it differs from rage in that it is evocable by atropinics and not

muscarinics. Paradoxically, arecoline with strychnine produced hallucinatory behavior.

Department of Pharmacology
The Chicago Medical School
Chicago, Illinois

228 Wada, Juan A. Behavioral and EEG correlates of modified levels of brain neurohumoral agents. Journal of Neuropsychiatry, 1963, 4, 251-254.

An evaluation of the central action of DOPA (3,4-dihydroxyphenylalanine), 5-HTP (5-hydroxytryptophan), iproniazid, and diphenhydramine, all of which are known modifiers of levels of brain neurohumoral agents, has revealed significant behavioral and electroencephalographic data in cats and monkeys. The administration of DL-DOPA along with vitamin B_6 the coenzyme for DOPA decarboxylase, produced a marked alerting effect in both cats and monkeys. Administration of 5-HTP along with vitamin B_6 produced a marked deleterious effect on both conditioning avoidance and approach behavior. When DOPA and 5-HTP are combined, the behavioral effects appear to be entirely dependent on the dose relationship between the two agents; i.e., the overall effect is determined by the agent given in larger amount. The administration of reserpine to iproniazid-pretreated animals produced deleterious effects in avoidance performance of cats but no visible effect on approach behavior of monkeys while administration of diphenhydramine produced a marked restlessness, some incoordination, and a constant wobbling movement of the head. Studies also revealed that reserpine, regardless of the route of administration, produced a marked deleterious effect on conditioned avoidance performance of cats. Electrographic observations with DOPA revealed a marked activation pattern while 5-HTP was correlated with slower waves of higher voltage and this effect was completely blocked by atropine.

Kinsmen Laboratory of Neurological Research
University of British Columbia
Vancouver, Canada

229 Wada, J. A., Wrinch, J., Hill, D., McGeer, P. L., McGeer, E. G. Central aromatic amine levels and behavior. I. Conditioned avoidance response in cats, following administration of psychoactive drugs or amine precursors. Archives of Neurology, 1963, 9, 69-80.

Using the intraventricular route of administration, various centrally active drugs and drug combinations, with one exception, produced depression of learned performance in cats. Conditioned avoidance response in 8 cats studied over a period of 2½ years was used as a behavioral measure to test the effect of a large number of centrally active drugs. Both intraperitoneal and intraventricular administration was used. Limitations of the latter for the purpose of evaluating central action is discussed. By the intraperitoneal route, drugs or precursors designed to create a decrease in catecholamine content, or an increase in serotonin had a deleterious effect on performance; those designed to decrease serotonin or increase catecholamine content tended to facilitate performance. Detailed behavioral descriptions associated with each drug and drug combination are provided. The results are related to previous work and to mechanisms of brain amine influence. It is suggested that the maintenance of an intricate equilibrium among various endogenous neurohumoral agents rather than changes in the absolute level of a particular agent is of primary importance for the learned performance of avoidance behavior. (13 Refs.)

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University of British Columbia
Faculty of Medicine
Vancouver, Canada

230 Frankenhaeuser, Marianne, & Jarpe, Gundla. Psychophysiological changes during

infusions of adrenaline in various doses. Psychopharmacologia, 1963, 4, 424-432.

Effects of intravenously infused l-adrenaline on psychological and physiological variables were studied in male volunteers. The changes in heart rate, blood pressure, and subjective stress were pronounced with increasing dose levels of the drug. Concomitant improvement in a performance test was slight. To examine the physiological and subjective reactions and objective performance, 5 medical students, aged 21-28 years, were given isotonic solutions containing 2 mg adrenaline as base per ml continuous intravenous drip. The two most overt symptoms were tremor and facial pallor. The subjects also reported palpitation, dryness of mouth, numbness of limbs, pounding in the head, chest, or abdomen, feelings of unreality, headache, and nausea. While the physiological changes remained relatively constant throughout the infusion period, the subjective reaction decreased toward the end of the infusion. In the placebo condition, there were fairly large differences between the subjects in the physiological variables. Results of the memory test revealed no consistent effects of adrenaline. The change in performance although rather small was in the direction of improvement with increasing doses of adrenalin. Although some distinctly unpleasant and disagreeable sensations were produced by the experiments, true anxiety or panic was not experienced. (16 Refs.)

Psychological Laboratory
University of Stockholm
Sweden

231 Kozlovskaya, M. M., & Val'dman, A. V. Izucheniye deystviya neyrotropnykh sredstv na povedencheskiye reaktsii dientsefalicheskogo urovnya. (Study of the effect of neurotropic drugs on behavioral reactions at the diencephalic level.) In: Val'dman, A. V. (Ed.). Aktual'nyye problemy farmakologii retikulyarnoy formatsii i sinapticheskoy peredachi. Leningrad: I Leningradskiy Meditsinskiy Institut imeni Akademika I. P. Pavlova, 1963, 116-114.

For psychopharmacological research, it is very important to study the effect of neurotropic drugs on different sections of the brain referring to the integration of emotions and behavioral reactions. The hypothalamic area is most interesting among subcortical structures. Behavioral reactions were studied in rabbits after the cortical area was stimulated. The rabbit's head was rigidly fixed, and 3-5 to 12 electrodes were implanted. Unipolar stimulation for 30-60 seconds with an interval of 10-40 minutes was preferred to a bipolar stimulation. Not more than two electrodes were used during each experimental day. The response reactions (behavioral and emotional) occurring during stimulation of the hypothalamic areas were divided into three distinct types: 1) An initial reaction, "nonspecific" for each individual structure, was evoked by a minimal voltage. This reaction was characterized by an "alert" reaction in the posterior hypothalamic area and by "hypnotic" state in the anterior hypothalamic area; 2) A behavioral reaction (food reaction, search reaction, rage, and sleep), specific for each morphological structure, was evoked by an "optimal" stimulation of these structures. This reaction was characterized by excitation in the posterior hypothalamic areas and suppression and sleep in the anterior hypothalamic area; 3) A complex of motor manifestations ("nonspecific" motor reaction) was evoked by a maximal stimulation. Very small doses of chlorpromazine (0.01 mg/kg) and of morphine (0.005-0.01 mg/kg) suppressed the "alert" reaction and also the "hypnotic" state. Chlorpromazine in doses of 0.1-0.3 mg/kg eliminated all emotional elements of the response reaction and only purely motor manifestations remained. Very small doses of morphine (0.001-0.01 mg/kg) sharply reduced the "rage" reaction while somewhat larger doses completely inhibited the

reaction. The most effective doses with a motor reaction were 3-5 mg/kg for morphine and 0.5-2 mg/kg for chlorpromazine.

(No address)

232 Rushton, Ruth, Steinberg, Hannah, & Tinson, Christine. Effects of a single experience on subsequent reactions to drugs. British Journal of Pharmacology and Chemotherapy, 1963, 20, 99-105.

A single brief experience can markedly modify subsequent reactions to drugs; rats' activity depended on whether a second trial took place under the influence of drugs or placebo and also on the conditions of the first trial. The activity of rats was studied in an unfamiliar Y-shaped runway. The activity studied was the number of entries into the arms of the Y during a 3-minute trial, two trials being given 3 days apart. Thirty rats were injected with a saline placebo and 30 received a mixture of amphetamine sulfate (0.75 mg/kg) and amylobarbitone sodium (15 mg/kg). At the first trial, the drug mixture practically doubled activity. Each of the two groups were then divided in half and received a second injection. At the second trial, rats which had been under the influence of the drug mixture at the first trial were again made more active by the mixture, but the drug mixture did not increase the activity of rats which had received only saline at the first trial. The findings are suggested as congruent with the ways in which past experience can modify reactions to centrally acting drugs in man. The drug mixture also produced ataxia which was assessed by measuring the variability of footprint splay. Ataxia was unaffected by previous experience.

Department of Pharmacology
University College
London, England

233 Glasky, Alvin J. Effect of chorpromazine and physical activity on brain protein metabolism in vivo. Federation Proceedings, 1963, 22, 272. (Abstract)

The effect of chlorpromazine and physical activity on the incorporation of radioactive leucine-C^{14} into proteins in vivo was studied in rats. Rats were pretreated for 24 hours with 50 mg/kg chlorpromazine or an equivalent volume of saline. Five μc C^{14} in 0.1 ml was injected intracranially and one-half hour later the rats rested for 1 hour in an incubator or swam in water both kept at 30° C. The animals were decapitated and the matabolic fate of the isotope was followed in liver, muscle and six separate anatomical areas of the brain. Results showed that besides having an epinephrinelike effect on blood sugar, there was a significant inhibition of the incorporation of C^{14} into protein in all areas of the brain particularly the midbrain. Swimming tended to overcome the inhibition of leucine incorporation in the midbrain area caused by chlorpromazine.

Abbot Laboratories
North Chicago, Illinois

234 Malis, Jerry L., Ries, Mary Anne, & Bradley, Robert J. Further studies on the pharmacology of Wy-535. A new analgesic agent. Federation Proceedings, 1963, 22, 248.

Analgesic testing in rats and monkeys indicated that Wy-535 had analgesic effectiveness greater than that of codeine or pethidine and was without many of the side effects of narcotic analgesics. The effects of Wy-535 on minute volume, respiration rate were measured in unanesthetized dogs with chronic tracheal cannulae. Blood pressure and heart rate were recorded from both anesthetized and unanesthetized dogs through chronic indwelling arterial catheters. Direct addiction liability was studied in rhesus monkeys. The animals were given s.c. injections of Wy-535 every 6 hours for 37 days. On the 15th and 30th days, the animals were challenged with nalorphine 2 mg/kg s.c. On the 37th day, Wy-535 was abruptly terminated and the animals were observed for withdrawal symptoms. Suppression of morphine withdrawal symptoms was studied in morphine-addicted rhesus monkeys. The animals' regular morphine injections were withheld until withdrawal symptoms appeared; Wy-535 was then administered s.c. at 15 and 30 mg/kg.

Wyeth Laboratories Inc.
Radnor, Pennsylvania

235 Kupferberg, Harvey J., Burkhalter, Alan, & Way, E. Leong. A sensitive fluorimetric assay for morphine. Federation Proceedings, 1963, 22, 249. (Abstract)

Conversion of morphine to pseudomorphine, a highly fluorescent dimer of morphine, was used as a sensitive, quantitative assay for morphine in tissue extracts. Morphine was oxidized to pseudomorphine under alkaline conditions with potassium ferricyanide and as little as 0.02 μg/ml of morphine could be determined in a 5 ml sample of plasma. Extraction of morphine from plasma was by a slight modification of the method by Way et al. (1960). The recovery of morphine added to plasma exceeded 90 percent. Plasma blanks were negligible. This method was used successfully to determine plasma levels of morphine in rabbits following intravenous, intramuscular, and subcutaneous administration of morphine. Compounds which did not yield fluorescent products were the morphinans, codeine, diacetylmorphine, and dihydromorphinone.

Department of Pharmacology
University of California Medical Center
San Francisco, California

236 Lemberger, L., Kuntzman, R., & Conney, A. H. Synthesis of dopamine from tyramine in vitro. Federation Proceedings, 1963, 22, 388. (Abstract)

Tyramine is investigated as a possible precursor for catecholamine biosynthesis. Incubation of tyramine with rabbit liver homogenate yielded a compound which, upon subsequent oxidation with iodine, gave a product having the same activation and fluorescent spectra as oxidized dopamine. In the presence of TPN, glucose-6-phosphate and the soluble fraction of liver, enzyme activity was localized in the microsomes. To prove that the product formed was dopamine, C^{14} tyramine was incubated with rabbit liver microsomes, soluble fraction, and the above cofactors. The product formed was absorbed on alumina and was eluted with 0.2N acetic acid. The metabolite had the same mobility as authentic C^{14} dopamine in four chromatographic systems. Incubation of octopamine (norsynephrine) with the microsomal system yielded a compound having the same fluorescent characteristics as norepinephrine.

Albert Einstein College of Medicine
Bronx, New York

237 Kornetsky, Conan, & Kiplinger, Glenn F. Potentiation of an effect of morphine in the rat by sera from morphine-tolerant and abstinent dogs and monkeys. Psychopharmacologia, 1963, 4, 66-71.

Forty-eight hours prior to the administration of morphine sulfate (MS), rats were injected with serum from morphine-tolerant and control animals (dogs and monkeys). Sera from the tolerant animals considerably potentiated the effect of MS on the rats' motor behavior. No explanation is given of the nature of the potentiation. After receiving increasing doses of MS up to 60 mg/kg daily for 2 weeks, 5 mongrel dogs were abruptly taken off the drug. These dogs, as well as the controls, were exsanguinated and sera from each of them was prepared. Three mm of serum from donor animals (test as well as controls) were injected intraperitoneally into 114 male rats. Twenty mg/kg of MS was given to each of the rats 48 hours after serum injection. An increase in swim time of the rat was the criterion of effect of test doses of MS. The injection of serum of donors per se had no effect on gross behavior of the rats. Control swim times were the same in treated and untreated rats at first. At 30 and 60 minutes, mean swim time in seconds was significantly longer in rats with serum from morphine-tolerant donors. It was also shown that the serum from these donors increased the magnitude of a sublethal dose of MS in the rat. When test animals were pretreated with either control serum or serum from tolerant dogs and then challenged with previously determined LD50 of MS serum, neither antagonized nor potentiated the lethal effect of morphine. The metabolism rate and excretion of MS in the dog shows that no significant amount of MS remains in the blood 48 hours after MS administration. (3 Refs.)

Department of Pharmacology and
Experimental Therapeutics
Boston University School of Medicine
Boston 18, Massachusetts

238 Truitt, Edward B., Jr., Duritz, Gilbert, & Ebersberger, Ethel M. Evidence of monoamine oxidase inhibition by myristicin and nutmeg. Proceedings of the Society for Experimental Biology and Medicine, 1963, 112, 647-650.

Nutmeg and its active component myristicin show evidence of central MAO inhibition. For the purpose of estimating MAO inhibition by measuring the potentiation of tryptamine convulsions, graded doses of tryptamine HCl 0.5 percent solution were injected i.v. into 10 mice per dose level. The dependent variables in the experiment were: (1) Three seconds or more of clonic jerking, tremors, and/or side-to-side head movements to calculate the CD_{50} from dose-response lines, (2) estimation of palpebral ptosis, and (3) measurement of cerebral 5-hydroxytryptamine. Ground nutmeg was given orally. Chemically synthesized myristicin, the active component of nutmeg, dissolved in liquid petrolatum, was given orally or intraperitoneally. An optimum dose of 500 mg/kg of ground nutmeg gave evidence of tryptamine potentiation, while 1000 mg/kg showed reversal. (7 Refs.)

Department of Pharmacology
University of Maryland School of Medicine
Baltimore, Maryland

239 Weaver, Lawrence C., Mitchell, Frank E., & Kerley, T. Lamar. Toxicopathologic and pharmacologic properties of piperacetazine, a potent tranquilizing agent. Toxicology and Applied Pharmacology, 1963, 5, 49-60.

A study of the detailed toxicology and supplemental pharmacology of piperacetazine showed that the drug given continuously over 1 year was well tolerated by rats and dogs with no significant pathologic effects. Acute toxicity followed by death occurred in 2 dogs at 200 mg/kg i.v. Toxicity was investigated in 100 male and female mice, 64 albino rats, 200 weanling male and female rats, and 14 mongrel dogs. To determine chronic toxicity, the drug was administered continuously to rats at 0.005, 0.01, and 0.025 percent concentrations of their diets, and daily to dogs at 0.25, 1.0, and 5.0 mg/kg/day by capsules orally. Dogs receiving 1.0 mg/kg showed scleral congestion, slight ataxia and drowsiness after each dose of the drug but always recovered on the following day. Those receiving 5.0 mg/kg/day showed various degrees of depressed activity. In rats, no toxic effects could be associated with long-term oral drug administration. Acute toxicity was determined following intragastric administration to female mice and intragastric and intraperitoneal administration to male mice, rats, and mongrel dogs. No lethal effects were observed at i.g. administration of 50-100 mg/kg of the drug; however, i.v. administration of 200 mg/kg was lethal in 1 dog within 6 minutes and in another immediately. Oral doses of 50 mg/kg caused profound depression of activity in 3 dogs. At 8 days, 2 of the dogs were still ataxic and not eating and were sacrificed. Piperacetazine failed to alter the convulsant properties of Metrazol but did show moderately effective antihistaminic properties. (9 Refs.)

Research Center
Pitman-Moore Company
Division of the Dow Chemical Company
Indianapolis, Indiana

240 Pisano, John, Abraham, David, & Udenfriend, Sidney. Gamma-aminobutyryl-histidine in brain. Journal of Neuropsychiatry, 1963, 4, 264-265.

Homocarnosine, present only in the central nervous system, is excreted in the urine and therefore offers possibilities for studying metabolic processes of the central nervous system in intact animals and humans. The amount of homocarnosine in the central nervous system of various animal species and humans is presented. Homocarnosine parallels the distribution of gamma-aminobutyric acid, also found exclusively in the central nervous system. Carnosine was found in the central nervous system but in smaller amounts than homocarnosine. There was no hydrolysis of homocarnosine when glycyltyrosine was hydrolyzed by brain extracts. The dipeptide, found in human urine, was not of dietary origin.

National Heart Institute
National Institutes of Health
Bethesda, Maryland

241 De Barran, L., Gogolak, G., Longo, V. G., & Stumpf, Ch. The action of tryptamine upon the electrical activity of single hippocampal neurons. Journal of Pharmacology and Experimental Therapeutics, 1963, 139, 337-344.

Tryptamine consistently inhibited the firing of the pyramidal and subicular units, while producing an increase of the firing rate of two out of three granule cells. Hippocampal cells are very sensitive to tryptamine, pyramidal and subiculum cells being consistently inhibited while two out of three fascia dentate granule cells were consistently stimulated and one inhibited. Tryptamine resembles LSG, both resulting in a flattening of the cortical electrical activity and a disruption of the hippocampal theta waves. Tryptamine affects the vascular system and peripheral receptors similarly to 5-hydroxytryptamine. When there is a disruption of the theta waves, there is a decrease in the firing rate of pyramidal cells.

Consejo Nacional de Investigaciones
Cientificas y Tecnicas
Buenos Aires, Argentina

242 Orth, O. S., & Mackey, Jas. P. Laboratory evaluation of Indoklon. Journal of Neuropsychiatry, 1963, 4, 164-173.

Indoklon was shown to be a potent convulsive agent in Sprague-Dawley rats and in mongrel dogs. A laboratory evaluation of the use of Indoklon as a convulsive agent was presented, using rats and mongrel dogs as the specimens. Pathological changes resulting from the use of this convulsive agent were of particular interest. Those changes observed in the rat were minimal and were found to be no greater in the treated animals than in the controls. The only pathological changes noted in the dogs were one instance of focal liver necrosis, one of periductal lymphocytic infiltration of the liver and one of a fatty liver. Such changes would be possible from inadequate pulmonary ventilation and carbon dioxide accumulation secondary to the observed fluctuation of the blood pH. There were no significant changes in blood sodium, potassium, or calcium. EEG changes consisted of maximum seizure patterns. EKG changes revealed A-V nodal disassociation, complete heart block and extrasystoles. All changes were similar to those noted for other methods of convulsion therapy.

Department of Anesthesiology
University Hospitals
Madison, Wisconsin

243 Peng, M. T. Locus of emetic action of epinephrine and DOPA in dogs. Journal of Pharmacology and Experimental Therapeutics, 1963, 139, 345-349.

Perphenazine, effective against DOPA-induced emesis, did not prevent emesis induced by epinephrine. Epinephrine was 15 times more potent than DOPA in inducing emesis in dogs. There was no correlation between the elevation of emetic threshold to epinephrine and the elevation of the apomorphine threshold or completeness of trigger zone ablation. The same operation renders dogs completely refractory to DOPA-induced emesis. Gut denervation did not alter its threshold. The results suggest that DOPA, like apomorphine, provokes emesis only via the trigger mechanism. There was no difference in the anti-emetic effects of glycine against DOPA and epinephrine. Atropine had no effect against emesis induced by epinephrine. Perphenazine was effective in preventing DOPA-induced emesis, but not readily effective in preventing epinephrine-induced emesis.

Department of Physiology
National Taiwan University College of Medicine
Taipei, Taiwan

244 Gray, William D., Rauh, Charles E., & Shanahan, Robert W. The mechanism of the antagonistic action of reserpine on the anticonvulsant effect of inhibitors of carbonic anhydrase. Journal of Pharmacology and Experimental Therapeutics, 1963, 139, 350-360.

Catecholamines in the brain are necessary in order for inhibitors of carbonic anhydrase to exhibit their anticonvulsant effect. Antagonism of the anticonvulsant action of inhibitors of carbonic anhydrase in mice by reserpine was shown not to be due to any effect of this agent on the brain with respect to concentration of inhibitors, activity of carbonic anhydrase, intracellular localization of enzyme and inhibitor, or interaction of enzyme and inhibitor. Because methyldopa and tetrabenzine were also able to antagonize the action of methazolamide, depletion of brain amines seemed to be the causative factor.

Department of Experimental Pharmacology
Lederle Laboratories Division
American Cyanamid Company
Pearl River, New York

245 Stein, Larry. Anticholinergic drugs and the central control of thirst. Science, 1963, 139, 46-48.

Anticholinergic drugs evidently block drinking by a central effect and eating by a peripheral effect. Atropine and scopolamine were compared with their centrally inactive quaternary analogs,

atropine methyl nitrate and scopolamine methyl nitrate, for effects on water and food intake in rats. All drugs inhibited eating, but only the centrally active compounds inhibited drinking. The studies suggested strongly that, at least in the rat, muscarinic synapses in the hypothalamus are part of a brain system that regulates water intake and such synapses provide the likely sites of action for the drug effects reported in the study.

Wyeth Laboratories
Philadelphia 1, Pa.

246 Setnikar, Ivo, Murmann, Walter, & Magistretti, Maria J. Analysis of the antagonism between some brain stem stimulants and pentobarbital. Archives Internationales de Pharmocodynamie et de Therapie, 1963, 141, 199-209.

Some brain-stem stimulants have a life-saving activity in mice intoxicated with pentobarbital. Conversely pentobarbital has a life-saving activity in brain-stem stimulant intoxication. The antagonism between the two drugs is not of a competitive nature. Statistical methods were used to determine if the hypothesis of a reversible competitive antagonism between pentobarbital and bemegride is in agreement with results from acute toxicity tests. For antagonism to be competitive, it must be specific and be observable in several kinds of experiments; it must be overcome by increasing the dose of the agonist, and the molecules of the two drugs should be similar in shape. Though all criteria were met in this case the hypothesis did not seem valid. Counter arguments were that there was neither an equilibrium of concentration nor of effects of the two drugs in either the whole animal or the isolated organ. Also the values for the number of molecules of pentobarbital reacting with the receptor, the number of molecules of the stimulant reacting with the receptor, the pentobarbital-receptor equilibrium constant, and stimulant-receptor equilibrium constant, should not differ significantly, but actually they do. It is, therefore, concluded that even if experimental data fit formally into a theory, the physico-chemical mechanism of action of the competing drugs must also support both theory and test results. Since these mechanisms are unknown, the hypothesis of competitive antagonism cannot be safely formulated. (15 Refs.)

Recordati, S.P.A. Research Division
Milano, Italia

247 Dandiya, P. C. & Menon, M. K. Studies on central nervous system depressants (III). Influence of some tranquillizing agents on morphine analgesia. Archives Internationales de Pharmacodynamie et de Therapie, 1963, 141, 223-232.

Analgesia was obtained with sub-analgesic doses of morphine combined with Rauwolfia alkaloids and phenothiazine derivatives; meprobamate, carisoprodol, and diphenylmethanes were ineffective in raising the subthreshold dose of morphine. An experimental study in which tranquilizers of different chemical groups, namely, Rauwolfia group, phenothiazine derivatives, propane and butanediols, substituted amides, and other drugs were tested for their ability to increase the action of a sub-analgesic dose of morphine. Since measurement of pain involving deeper structures is important the mechanical compression method was employed in addition to two methods which measure superficial stimulation, the hot-wire and the hot-plate methods. Mice were used as subjects with the hot-wire method; rats with the other two. Average reaction times before administration were compared with average reaction times at various intervals up to 1 hour after treatment. The number of animals showing significant analgesia in ratio to the number of animals employed is given for all treatments. Probability was determined using Chi square. Sub-analgesic dosage of morphine for all three techniques was used to determine more accurately analgesia produced by the drugs. The three analgesiometric methods are described and possible mechanisms by which drugs may have exerted effects are discussed.

Department of Pharmacology, S.M.S.
Medical College
Jaipur, India

248 Aceto, M. C., & Harris, L. S. Effect of various agents on reserpine induced blepharoptosis. Federation Proceedings, 1963, 22, 626.

Selected compounds were tested for their ability to prevent and/or reverse reserpine-induced blepharoptosis in mice. At progressively increasing doses, imipramine and chlorpromazine could clearly be differentiated. Imipramine prevented and chlorpromazine increased ptosis. Phenoxybenzamine and oxypertine increased and dichloroisoproterenol reversed ptosis. The antihistaminics, antazoline, chlorpheniramine, diphenhydramine, tripelennamine and thenfadil were tested. All the antihistamines except antazoline had varying degrees of activity on the prevention and/or reversal tests. Antazoline, which is known to have sympatholytic effects, did not alter reserpine-induced ptosis. Drugs having a pronounced element of α-sympatholytic activity will tend to increase ptosis whereas the β-sympatholytic, DCI, shows amphetaminelike characteristics. Further, antihistamines will prevent and/or reverse reserpine-induced ptosis by some undetermined property(ies).

Sterling-Winthrop Research Institute
Rensselaer, N. Y.

249 Berry, C. A. & Hance, A. J. Patterns of excitability in cerebral cortex. Federation Proceedings, 1963, 22, 391.

This work deals with the examination of the superficial response of identical stimuli applied to the pial surface of anterior and posterior sigmoid, anterior and medial suprasylvian (MSS), lateral (LAT) and ectosylvian gyri in gallamine immobilized cats. Stimuli were adjusted to twice threshold and recordings taken 2 mm from the stimulus site. Relative amplitudes of the 2 evoked potentials were compared at intershock intervals of 16-400 msecs. Sensory regions of LAT and ectosylvian gyri showed facilitation of the second response by the first. Neuronally isolated islands of LAT showed no such facilitation. MSS responses showed minimal interaction until the interval approach 16 msecs. d-Amphetamine (2 mg/kg) or chlorpromazine (1-5 mg/kg) had little effect on interactions at either area. Pentobarbital (10-60 mg/kg) reduced the second/first ratio in a dose-related manner, particularly at the shorter intervals and especially at LAT. As a result interaction patterns from different areas became closely similar. Pentobarbital had no effect on interaction patterns in isolated cortex.

Department of Pharmacology
Stanford University
Palo Alto, California

250 Bhatnagar, R. K., & Reineke, E. P. Interactions between reserpine (R), 5-hydroxytryptamine, iproniazid (IP) and bromo-d-lysergic acid diethyl amide (BOL) as indicated by energy metabolism (M), body weight (W), adrenal (AD) weight, and thymus (TH) weight. Federation Proceedings, 1963, 22, 625. (Abstract)

Mature ovariectomized rats were injected daily for 32 days, singly and in various combinations with reserpine (0.2 mg/kg s.c.), 5-HT (12 mg/kg s.c.), BOL (0.5 mg/kg i.p.) and iproniazid (100 mg/kg i.p., initial dose, followed by 50 mg/kg every 4th day). In combined treatment, iproniazid was injected 2 hours before reserpine or 5-HT. Reserpine caused 50 percent mortality in 20 days, reduced metabolism rate 25 percent and weight 31 percent and increased adrenal and thymus weight. Concomitant iproniazid injection prevented mortality, decreased AD below controls, and reduced effect on M and W. Iproniazid alone caused transitory reduction in metabolism and body weight with normal adrenal weight. 5-HT produced transitory depression of energy metabolism and body weight with significant increase in adrenal over iproniazid but not over controls. Iproniazid + 5-HT induced significant increase in adrenal weight and decrease in thymus weight with thickening of dermis and loss of hair at injection site. Effect on metabolism and body weight was similar to that of iproniazid alone. Addition of BOL to iproniazid + 5-HT prevented these changes in dermis,

adrenal, and thymus weight, whereas BOL alone did not cause significant changes in the parameters measured. Antagonism of reserpine and facilitation of 5-HT action by iproniazid, particularly on adrenals, suggests that action of reserpine is by pathways other than 5-HT release.

Department of Physiology and Pharmacology
Michigan State University
East Lansing, Michigan

251 Bollard, B. M., Roizin, L., Sabbia, R., & Horwitz, W. A. Distribution of free and S^{35} labelled prochlorperazine (Compazine) in mammalian tissues. Federation Proceedings, 1963, 22, 317. (Abstract)

1. Short term experiments: (A) Intraperitoneal injection in rats, 5 mg prochlorperazine/100 g. Highest amounts were found in the lungs (300 μg/g) after 14 hours, then liver and kidney; concentrations in brain areas were lower. (B) Intravenous injection, 2.5 mg prochlorperazine S^{35}/100 g were given to rats and monkeys. In rats accumulation was greatest in liver (100 μg/g after $6\frac{1}{2}$ hours, and in cerebral tissues at 1 hour (65-92 μg/g). Values for monkey tissues were higher, most in the liver 159 μg/g) and temporal cortex (154 μg/g) at 1 hour. Total distribution of PCP S^{35} from radioactivity indicated significant metabolism or binding of PCP in rat tissues but very little in monkey tissues. 2. Long term experiments: (A) Rats received injections of 0.5 mg of PCP/100 mg intramuscularly daily for 2.6 and 12 weeks and subcutaneously for 6 and 12 months. Highest amounts were found in the adrenals throughout, and gradually increased in the lungs over the 12-month period. 3. Rats were pretreated with PCP as in 2.(A) for 6 months, then injected intravenously as in 1.(B). Distribution was similar to that in normal rats but all values were higher. Amounts in the liver fell off more slowly with time. Measurements of radioactivity suggested that less PCP S^{35} was metabolized and/or bound.

New York State Psychiatric Institute
Columbis University
New York, New York

252 Bush, Milton T., & Parrish, Herman. Methylation of barbiturates in vivo. Federation Proceedings, 1963, 22, 480. (Abstract)

Deininger (1955) established that norhexobarbital in mice can be converted to hexobarbital. By use of paper chromatography, Deininger showed considerable hexobarbital present in the blood 1-2 hours after injection of 200 mg/kg norhexobarbital. Precise fractional extraction and spectophotometry were applied to the determination of these drugs in whole mice. In male DUB/ICR mice less than 5 percent of a 1 mg i.v. dose of norhexobarbital is present as hexobarbital 1 hour after injection.

Department of Pharmacology
Vanderbilt University
Nashville, Tennessee

253 Chen Lin, Chih-Chia. Metabolic conversion of anileridine to normeperidine. Federation Proceedings, 1963, 22, 481. (Abstract)

Male Sprague-Dawley rats were given 15 mg/kg anileridine i.p.; 24-hour urine samples were extracted with benzene at pH 11. The benzene extract, after purification and concentration, was subjected to paper and to thin-layer chromatography. Both techniques revealed the presence of normeperidine. The substance having the same Rf as that of normeperidine was eluted from the paper chromatogram and subjected to countercurrent distribution. The distribution curve was found to be similar to that of authentic normeperidine treated in the same manner. In addition to normeperidine the chromatographic studies revealed the presence of free and acetylated anileridine. The quantities of the three compounds were determined after further purification of the urinary benzene extract by selective extraction at various pH's. The percentages of the dose administered of the 3 compounds excreted in 24 hours in 3 separate experiments were: anileridine, 0-0.4 percent, acetylanileridine, 0.6-1.2 percent and normeperidine, 6.1-8.3 percent. Furthermore, normeperidine was found in the urine from rats receiving acetylanileridine, indicating that N-dealkylation of the

nitrogen-ethylaniline bond of anileridine occurs also after acetylation.

University of California
Schools of Pharmacy and Medicine
San Francisco, California

254 Rosell, Sune, Sedvall, Goran, & Ullberg, Sven. Distribution and fate of dihydroxyphenylalanine-2-14C (Dopa) in mice. Biochemical Pharmacology, 1963, 12, 265-269.

A study of the distribution in whole mice of i.v. dihydroxyphenylalamine-2-^{14}C (dopa) with autoradiographic technique showed that radioactivity accumulated in the pancreas, various other organs and the adrenal medulla. While it disappeared later from most tissues, it could still be found after 4 days in the adrenal medulla. White adult mice were injected with 0.3 mg ^{14}C-dopa. It was rapidly taken up by various tissues. Five minutes after injection it was found in highest concentration in the pancreas, followed by the gastric mucosa, kidney adrenal medulla, intestinal mucosa, salivary glands, bone marrow and liver. After 1 hour the activity had increased tremendously in the adrenal medulla. After 4 hours the adrenal medulla dominated the distribution picture. Chromatography revealed that in the pancreas most of the activity was related to dopa, but some of it was found in the dopamine fraction. In the adrenal medulla, a labeled dopamine and noradrenaline could be identified 30 minutes after administration. Four days after ^{14}C-dopa injection radioactivity in the adrenal medulla represented mostly adrenaline but also some noradenaline. (13 Refs.)

Department of Pharmacology
Karolinska Institutet and Veterinarhogskolan
Stockholm, Sweden

255 Day, M. D., & Rand, M. J. Evidence for a competitive antagonism of guanethidine by dexamphetamine. British Journal of Pharmacology, 1963, 20, 17-28.

Studies were made of the interaction of guanethidine and dexamphetamine to determine whether these drugs act at the same site on cat nictitating membrane, rabbit ileum, guinea pig isolated vas deferens and rabbit heart and spleen. Estimation of levarterenol tissue content was done with the spectrofluorometric methods of Cass and Spriggs (1961). Dexamphetamine antagonized the sympathetic nerve block by guanethidine in the isolated sympathetically innervated rabbit ileum: the evidence suggested that the antagonism was competitive. Dexamphetamine antagonized the sympathetic nerve block by guanethidine in the isolated hypogastric nerve-vas deferens preparation of the guinea pig. Doses of dexamphetamine, larger than those required to antagonize the blocking action of guanethidine, abolished the responses of the nictitating membrane, ileum and vas deferens to nerve stimulation. Dexamphetamine did not influence the depletion of levarterenol by guanethidine in the heart and spleen of rabbits. The hypothesis is advanced that both dexamphetamine and guanethidine act on the store of levarterenol at sympathetic nerve endings.

Department of Pharmacology
School of Pharmacy
University of London
Brunswick Square, London, W. C. 1.
Great Britain

256 DeKornfield, Thomas J., & Lasagna, Louis. WIN 20740, a potent new analgesic agent. Federation Proceedings, 1963, 22, 248.

WIN 20740 (2-cyclopropyl-methyl-2'-hydroxy-5, 9-dimethyl-6, 7-benzomorphan) is a potent narcotic antagonist in animals, but an analgesic in man. In double-blind clinical studies of postoperative pain, relief indistinguishable from that provided by 10 mg morphine s.c. was reported with s.c. doses of WIN 20740 as small as 0.25 mg. Studies of postpartum pain indicate that analgesia after 0.25 mg WIN 20740 p.o. is significantly greater than that achieved with placebo and not significantly different from that obtained with Darvon Compound-65. Certain side effects (sedation, euphoria,

drunkenness, confusion and disorientation) were frequently seen after 2 mg p.o. or s.c. but side effects of any kind were rare at lower doses. Respiratory studies in volunteers, using carbon dioxide challenge, indicate that WIN 20740 at doses of 0.25 or 1 mg s.c. depresses breathing as much as does 10 mg of morphine.

Baltimore City Hospitals
Baltimore, Maryland

257 DeSalva, S. J., & Monteleone, V. J. Electrically-induced skin twitch assay for analgesimetry. Federation Proceedings, 1963, 22, 248.

Suppression of an electrically-induced skin twitch in rabbits has been employed as a means of evaluating analgesic drugs. The twitch is elicited by the topical application of bipolar platinum electrodes to the freshly-shaved skin. Four concentric areas (two on each side of the middorsal line) are marked off. The stimuli are delivered by a Thomas square stimulator at 120 cps with a pulse duration of 0.5 milliseconds. The end points used are: (1) the onset time for the twitch to occur following stimulation at a fixed intensity, which is just at the threshold level, and (2) the voltage requirment for the twitch response to occur within 1 second after application of the stimulus. Both types of measurement are made in duplicate at two test sites and appear to be related to each other. Morphine, codeine, Versidyne, acetylsalicylic acid, phenacetine, paracetamol, and several local anesthetics were evaluated. Both the narcotic and nonnarcotic drugs were effective at levels which did not produce any obvious neurotoxic symptoms. The method appears to lend itself to the rapid screening of potential analgesics.

Pharmacology Section
Colgate-Palmolive Research Center
New Brunswick, New Jersey

258 Pfeiffer, Carl C., Goldstein, Leonide, Munoz, Carlos, Murphree, Henry B., & Jenney, Elizabeth H. Quantitiative comparisons of the electroencephalographic stimulant effects of deanol, choline, and amphetamine. Clinical Pharmacology and Therapeutics, 1963, 4, 461-466.

Deanol (2-dimethylaminoethanol) and amphetamine both had a statistically significant stimulant effect on rabbits and humans in studies using the quantitative EEG method. In humans deanol had an immediate effect, while there was a latent period on rabbits. It acted in humans through mechanisms which can be acutely saturated. Choline and placebo controls were applied in these studies. Results of former tests were confirmed that the encephalographic effect in rabbits of i.v. administration of deanol (2-dimethylaminoethanol) occur after a latent period. A decrease in electrical energy of the EEG was observed due to pretreatment of the rabbits with pentobarbital. 1 mg/kg amphetamine in rabbits and 15 mg oral dose in humans caused a reduction in encephalographic variability, while deanol caused either an increase or no change at all. Choline had no significant effect on the CNS. These results show again that deanol is a mild central stimulant. The mechanism through which it acts in humans can be acutely saturated, pointing to the possibility that it is a provitamin or vitamer acting only after transformation in the body. It may therefore have a clinical effect only on those who do not have adequate levels of it. It is not clear if it is a precursor of acetylcholine. Deanol has had greatest success in the treatment of behavioral disorders in children, probably because of their rapid growth, excess activity, and dietary habits. (13 Refs.)

Bureau of Research in Neurology and Psychiatry
Princeton, New Jersey

259 Jurgelsky, William, Jr., & Thomas, James A. The effect of gamma-amino butyric acid on the toxicity of several organic phosphate insecticides. Federation Proceedings, 1963, 22, 189.

The effect of gamma-amino butyric acid (GABA) on the toxicity of several organic phosphate cholinesterase inhibitors was

explored. GABA in a single dose (0.2-1.0 g/kg i.p.) had negligible effects on the onset of symptoms and survival of rats given parathion (4-10 mg/kg p.o.). In rats receiving higher levels of GABA (2 g/kg i.p. or 2-5 g/kg p.o.) in conjunction with the above doses of parathion, the onset of typical cholinergic cymptoms was delayed and survival time at the upper doses of parathion was increased. Comparable effects on symptoms and survival times were seen in rats given multiples of oral LD 50 dose of parathion when large multiple doses of GABA p.o. or i.p. were administered alone or in conjunction with repeated small doses of atropine (2 mg/kg/hour i.p.). In preliminary studies on rats and chickens with malathion and EPN, GABA treatment was associated with decrease in mortality. While these findings are consistent with a CNS inhibitory effect for GABA, a more specific role cannot be excluded.

Department of Pharmacy
Food and Drug Administration
U. S. Department of Health, Education, and Welfare
Washington, D. C.

260 Khan, Akhlaque U., Forney, R. B., & Hughes, F. W. Effect of tranquilizers and stress on plasma free fatty acids in rats. Federation Proceedings, 1963, 22, 568.

Meprobamate (50, 100 and 200 mg/kg), chlordiazepoxide (15, 20 and 50 mg/kg), hydroxyzine (5, 10 and 20 mg/kg), chlorpromazine (1, 5 and 10 mg/kg) and reserpine (0.1, 0.5 and 1 mg/kg) were administered i.p. to fasting female rats and the plasma FFA determined 1 hour later (2 hours later in case of reserpine) by the method of Dole. Twenty and 50 mg/kg doses of chlordiazepoxide and all 3 doses of meprobamate decreased the plasma FFA significantly; chlorpromazine produced a decrease with 1 mg/kg, no change with 5 mg/kg and an increase with 10 mg/kg dose. The other tranquilizers did not alter the plasma FFA significantly. In another series of experiments, fed female rats were subjected to 50-volt electric shocks of 2 seconds duration, every minute for 1-1/2 hours. One group was pretreated with saline and the others with the intermediate dose of each of the tranquilizers 1/2 hour (1-1/2 hours in the case of reserpine) before shock. Following shock, plasma FFA increased in saline pretreated rats (0.729 vs 0.489 mEq/L in unshocked controls). Pretreatment with each of the tranquilizers completely prevented this increase in the plasma FFA.

Indiana University School of Medicine
Indianapolis, Indiana

261 Kornetsky, Conan. The effects of repeated administration of "LD 50" doses of drugs in drug-resistant mice. Federation Proceedings, 1963, 22, 511. (Abstract)

The purpose of this experiment was to determine if Swiss mice selected by their ability to survive a predetermined LD50 dose of a drug would show repeated resistance to the same dose of that drug, and if animals resistant to one drug were resistant to other drugs. Three drugs were studied: pentetrazol, strychnine, and pentobarbital. All injections were i.p. at 1-week intervals, and both male or female mice were used. With both strychnine and pentobarbital the second injection of the same dose of each drug to the survivors resulted in a significant decrease in the percent of animals surviving. When strychnine was given to pentobarbital-treated animals, the percent of animals surviving was significantly greater than the percent of drug-naive animals surviving, after the same dose of strychnine. However, when pentetrazol was given to pentobarbital-treated animals, the percent of animals surviving was significantly less than the percent of drug-naive animals surviving after the same dose of pentetrazol.

Boston University Medical Center
Boston, Massachusetts

262 Kuehn, Alfred, & Schallek, William. Effects of drugs on after-discharge in central lateral nucleus of cat. Federation Proceedings, 1963, 22, 392. (Abstract)

Stimulation of intralaminar nuclei in the thalamus of cats produced signs resembling petit mal epilepsy in man. Three anti-convulsant drugs and saline were tested on after-discharges induced by stimulation of intralaminar central lateral nucleus (CLN) and parietal cortex in cats prepared by ether-C^{14} technique. Diphenylhydantoin, clinically useful in grand mal epilepsy, depressed the cortex but not the CLN at 10 mg/kg i.v. Trimethadione, useful in petit mal epilepsy, depressed the CLN but not the cortex at 100 and 400 mg/kg. Chlordiazepoxide depressed CLN but not the cortex at 10 mg/kg; at 40 mg/kg this drug also depressed the cortex.

Hoffmann-La Roche, Inc.
Nutley 10, New Jersey

263 Lim, R.K.S., Guzman, F., Goto, K., Braun, C., & Rodgers, D. W. Evidence establishing central and peripheral sites of action for narcotic and nonnarcotic analgesics respectively. Federation Proceedings, 1963, 22, 249.

Analgesics will block the pseudaffective response, including vocal manifestations of visceral pain, evoked by i.a. injection of bradykinin (BK) into the spleen and other organs. When the vasoisolated but neurally intact spleen of a recipient dog (R) is perfused by a donor dog (D), R's vocalization to BK injected i.a. into R's spleen is blocked by the i.v. administration of non-narcotic analgesics (acetylsalicylic acid, sodium salicylate, paracetamol, phenylbutazone, oxyphenbutazone) to D, but not by the i.v. injection of narcotic analgesics (pethidine, morphine, levorphan) to D. The narcotic analgesics, however, block R's vocalization to BK when given i.v. to R, while the non-narcotic analgesics are ineffective, administered in this way. Injection of BK into R's spleen i.a. evokes discharge of potentials in R's splenic nerve. This discharge is blocked by administering acetylsalicylic acid i.v. to D but not by giving morphine i.v. These results provide evidence that the non-narcotic analgesics block the chemoreceptors of the primary neurons for vocalization and pain at the periphery, while the narcotic analgesics block synaptic transmission in the afferent relays for vocalization and pain in the CNS.

MSRL, Miles Laboratories, Inc.
Elkhart, Indiana

264 Matsumoto, C., & Horita, A. Studies of the antagonism of guanethidine by methamphetamine. Biochemical Pharmacology, 1963, 12, 295-297.

Because of the competition between guanethidine and methamphetamine, there is a decreased uptake of guanethidine by tissue. This decreased uptake results in a lesser degree of catecholamine depletion from cardiac tissue. New Zealand white rabbits of either sex were injected i.v. with an aqueous solution of guanethidine, an antihypertensive agent. Methamphetamine was injected intraperitoneally. The degree of depletion of catecholamine was measured in cardiac tissue. The results show that methamphetamine effectively antagonizes the depletion of catecholamine by guanethidine and the uptake of the latter by tissue. The antagonism of guanethidine by methamphetamine is probably not due to bretylium-like action, i.e., the inhibition of release of the neurohumoral agent from the terminal of the adrenergic neuron. It is suggested that methamphetamine itself causes the release of the catecholamine. Other investigators have reported that methamphetamine antagonizes the adrenergic neuronal blocking agents and the sympathomimetic amines for receptors. (11 Refs.)

University of Washington
School of Medicine
Seattle, Washington

265 Maynert, E. W. Specificity in the penultimate (ω-1) oxidation of barbiturates. Federation Proceedings, 1963, 22, 479. (Abstract)

The metabolic fate of 5-ethyl, 5-n-hexyl-barbituric acid was studied in dogs

receiving 15 mg/kg daily. Fourteen ether-extractable metabolites accounting for 55 percent of the dose were isolated in a 200-tube countercurrent distribution apparatus. The ω-1 alcohol amounted to 16 percent, and the ω-1 ketone, to 7 percent of the dose. The neutral metabolite fraction included three other alcohols (4.5 percent of the dose), one other ketone (2 percent) and a compound (1 percent) which upon acid hydrolysis yielded an unknown dialkylbarbiturate. Four more derivatives were found in the lipophilic end fraction (1 percent) but were not investigated further. The acidic metabolite fraction contained the oxidation product (3 percent), a hydroxy acid (1.5 percent) and the β-oxidation product (14 percent). No evidence for the presence of monoalkyl or N-alkyl metabolites was obtained. Glucuronide conjugates of the alcoholic metabolites were present only in small quantities. The isolation of several alcohols and ketones prove that oxidation is not restricted to the ω-1 carbon atoms of barbiturates. This finding is in harmony with other evidence suggesting a low degree of specificity for the microsomal hydrozylating enzymes.

Johns Hopkins School of Medicine
Baltimore, Maryland

266 Mazel, P., & Hernandez, P. Metabolism of N-phenylbarbital (Phetharbital). Federation Proceedings, 1963, 22, 479. (Abstract)

The metabolic fate and distribution of N-phenylbarbital (NPB) has been studied in male Nelson rats (50 mg/kg) and a human (1 mg/kg). Rat tissue analysis indicated that NPB was rapidly distributed in all tissues analyzed. NPB and its metabolites were isolated from the urine by differential solvent extraction and identified by UV spectra. In addition, NPB and its metabolites were characterized by thin-layer chromatography and identified as (1) unchanged NPB, (2) p-OH-NPB, and (3) the glucuronide of p-OH-NPB. The R_f values of compounds (1) and (2) were identical with those of authentic NPB and p-OH-NPB. Analysis of 24-hour human urine samples indicated that 0.5 to 1.0 percent of the administered dose was excreted as unchanged NPB.

Department of Pharmacology
The George Washington University School of Medicine
Washington, D. C.

267 Migdal, Walter & Frumin, Jack M. Amnesic and analgesic effects in man of centrally acting anticholinergics. Federation Proceedings, 1963, 22, 188. (Abstract)

Benztropine (6-8 mg) was given i.v. 60-120 minutes before induction of anesthesia to 14 otherwise healthy patients undergoing elective operations. Pentobarbital (50-150 mg) and 0.4 mg atropine were given i.m., 1 hour before induction. Anesthesia was begun with 0.2-0.3 g thiamylal i.v., maintained with various inhalation agents and often supplemented with muscle relaxants. All patients had complete amnesia for events in the preinduction period and for about 6 hours postoperatively. Four subjects required no analgesics postoperatively while 10 needed an initial dose of 50 mg pethidine on an average of 5 hours postoperatively.

Department of Anesthesiology
Beth El Hospital
New York, New York

268 Moore, K. E. Endogenous catecholamines and amphetamine toxicity in aggregated mice. Federation Proceedings, 1963, 22, 310 (Abstract)

The effects of d- and l-amphetamine sulfate (d-A and l-A) were studied in isolated and in aggregated (4/cage) mice. Intraperitoneal LD_{50}'s under isolated and aggregated conditions were 97 and 25 mg/kg respectively for d-A, in contrast with 150 and 125 mg/kg for l-A. In isolated mice, d-A reduced the brain and heart contents of levarterenol; aggregation markedly enhanced this effect. Pretreatment with phenoxybenzamine (10 mg/kg) or with chlorpromazine (2 mg/kg) reduced the percent mortality and levarterenol depletion in the d-A aggregated mice. Pretreatment with monoamine oxidase inhibitors had a potentiating effect while pretreatment with reserpine or α-methyl-m-tyrosine protected against d-A toxicity in aggregated

mice. In contrast to the effects of d-A, l-A produced only slight reduction in the tissue levarterenol content, and this effect was not markedly enhanced by aggregation. The release of endogenous levarterenol by d-A and the ability of aggregation stress to potentiate this release, play important roles in the increased toxicity of d-A in aggregated mice.

Department of Pharmacology and Toxicology
Dartmouth Medical School
Hanover, New Hampshire

269 Neff, Norton H., & Rossi, G. Victor. Distribution and metabolism of mescaline-C-14 in the cat brain. Federation Proceedings, 1963, 22, 335. (Abstract)

Serial coronal sections were made of the brains removed from cats at various time intervals after i.v. injection of mescaline-2'-C^{14}-HCl. The sections were placed on no-screen X-ray film, frozen and placed in a dry CO_2 atmosphere for 30 days. Analysis of the resulting autoradiograms indicated selective distribution of radioactive material. Relatively high activity was present in the cortical gray matter, areas associated with vision (lateral geniculate, superior colliculus) and auditory areas (medial geniculate). Radioactive compounds in cat brain sections were extracted, chromatographed, and analyzed. Mescaline and an α-hydroxy acid, tentatively identified as 3,4,5-trimethoxymandelic acid, were found. The behavioral changes observed in the cat following mescaline may be related to the presence of a metabolite, 3,4,5-trimethoxy-mandelic acid, or an intermediate such as β-hydroxy-β (3,4,5-trimethoxyphenyl) ethylamine (hydroxy mescaline). These compounds are structurally similar to metabolites of norepinephrine and may influence the metabolism of norepinephrine or its precursors in the brain.

Philadelphia College of Pharmacy and Science
Philadelphia, Pennsylvania

270 Mingioli, Elizabeth S., & Kory, Mitchell. Some characteristics of hydrazine amine oxidase inhibitors. Federation Proceedings, 1963, 22, 389.

Some characterists of hydrazine amine oxidase inhibitors. Mitochondrial MAO and soluble tyramine oxidative deaminase (TOD) from Sarcina lutea catalyze identical reactions. Both enzymes are inhibited by numerous hydrazines which are greatly enhanced by cyanide; non-hydrazines are not affected by cyanide. At the temperature and pH usually employed in manometric estimation of amine oxidase activity, all hydrazines tested were found to inhibit MAO and TOD even though the inhibitors were confined to the center well of the Warburg flask. The effect of equilibration cyanide and hydrazine compounds, or inhibitors derived from them, distill from one solution into all others in the reaction vessel. With hydrazine inhibitor at pH 11.5 in the center well, no inhibition occurred, whereas maximal inhibition was observed between pH 6.5 and 9.5.

Lilly Research Laboratories
Indianapolis, Indiana

271 Oberholzer, R. Contribution a l'etude d'une eventuelle action teratogene de l'imipramine (Tofranil). (Contribution to the study of possible teratogenicity of imipramine (Tofranil). Medecine et Hygiene, 1963, 591, 358.

Contribution to the study of possible teratogenicity of imipramine (Tofranil). The article by Robson appearing in Lancet, March, 1963, concerning imipramine's influence on fetal malformations in rabbits is critically reviewed, and results negative to teratogenicity presented for imipramine in "another laboratory animal," is also considered. Mention is also made of Millen's (1962) finding that even such products as caffeine and nicotine may cause fetal malformation. There is no evidence to point to teratogenic toxicity for imipramine and a critical review of

over 1300 publications in the world literature on the clinical use of imipramine have failed to show that it has any influence on the development of the human embryo. (2 Refs.)

Service Medical
J. R. Geigy SA
Basel, Switzerland

272 Parisi, Alfred F., & Raines, Arthur. Diphenylhydantoin suppression of repetitive activity generated in nerve endings. Federation Proceedings, 1963, 22, 390.

Diphenylhydantoin suppression of repetitive activity generated in nerve endings. In chloralozed cats, the soleus nerve was stimulated and neural activity recorded antidromically from a corresponding ventral root filament containing a single active axon. The application of a tetanic stimulus (400/second for 10 seconds) to the peripheral nerve, regularly causes each subsequent response to a single stimulus to become repetitive. This post-tetanic repetitive activity (PTR) which originates in motor nerve terminals (m.n.t.) is suppressed by diphenylhydantoin 5 mg/kg, i.v. and abolished by 20 mg/kg, i.v. This dose range coincides with the anticonvulsant range in the cat. PTR suppression usually is manifest within 20 minutes and is maximal by 90 minutes after injection. The effect of diphenylhydantoin on neuromuscular transmission was gauged by its effect on isometric twitch response to single maximal nerve volleys. In these experiments the PTR of m.n.t. caused a contractile post-tetanic potentiation (PTP). Accordingly 20 mg/kg diphenylhydantoin i.v. does not diminish the control twitch but abolishes PTP. The specific depression of PTR generation in m.n.t. without disruption of transmission furnishes a possible explanation of the anticonvulsant action of diphenylhydantoin.

Department of Pharmacology
Cornell University
Ithaca, New York

273 Prabhu, Venkatray G., Browne, Roland K., & Zaroslinski, John F. Pharmacological turnover in mouse and rat of a new hypnotic-methaqualone. Federation Proceedings, 1963, 22, 539.

In this study the rate of metabolic turnover of (2-methyl-3-orth-tolyl-4(3H)-quinazolone hydrochloride (I)) orally administered to the rat and mouse, and the role of the liver and kidney in the biotransformation of (I) have been determined on the basis of sleeping time studies. Using this criterion in the rat, (I) is found to be metabolized at a rate of just below 10 mg/kg/hour, and in the mouse between 12.5-15 mg/kg/hour. Rats and mice pretreated with SKF 525-A, a liver microsomal inhibitor, showed a great enhanced sleeping time. Thus, 100 mg/kg of (I) which produces in the normal rat and mouse a sleeping time of 104 and 77 minutes respectively, produced a sleeping time of more than 10 hours in each species after pretreatment with 50 mg/kg of SKF 525-A. Similar results were also obtained with (I) when the liver was acutely injured with CCl_4. The kidney did not seem to play a significant part in the biologic inactivation of (I), since neither unilateral nor bilateral nephrectomy of the animals altered the sleeping time from that of normal animals treated with (I).

Arnar-Stone Laboratories, Inc.
Mount Prospect, Illinois

274 Roszkowski, Adolph P., Kacmarik, Elaine D., & Jacobs, Louise. Central muscle relaxant properties of some mono- and dihalo-2-aminobenzoxazoles. Federati Proceedings, 1963, 22, 627.

Although numerous studies relating to the central muscle relaxant properties of zoxazolamine have appeared, other halo-substituted analogs in this series have not been examined extensively. The dose of zoxazolamine which produces a 50 perce loss of righting ability (PD_{50}) is 81 mg/

in mice i.p. and 415 mg/kg p.o. The 6-Cl or 5- or 6-Br substituted analogs were found to approximate the same potency. They were more potent and displayed a greater margin between paralytic and lethal dose levels than did the 5-F or -I substituted agents. The 5-Cl, 6-Br analog was also in this potency range, but the 5-Br, 6-Cl analog was decidedly less active in the mouse with PD_{50}'s of 350 mg/kg, i.p. and 740 mg/kg, p.o. Surprisingly, this agent was found to be remarkably active in the rat in that the oral PD_{50} is 59 mg/kg or only 1/12 of the mouse oral PD_{50} and 1/6 of the mouse i.p. PD_{50}. Likewise the 5,6-dichloro analog is only moderately potent in both mice and rats i.p., but very potent p.o.

McNeil Laboratories, Inc.
Fort Washington, Pa.

275 Sabelli, H. C., Marks, R., & Toman, J. E. P. Drug studies on earthworm isolated ventral cord. Federation Proceedings, 1963, 22, 391. (Abstract)

Drug effects were studied on the 2-unit spikes of the ephaptic fiber system of Lumbricoides terrestris, using conventional and phase-plane (voltage vs. rate of change) recording. Threshold-raising blockers (1 mM or less) included: phenothiazines (flupenazine, triflupromazine, thiopropazate, thioridazine, perphenazine), antidepressives (amitriptyline, desipramine, opipramol), homochlorcyclizine, nicotine and procaine. Chlordiazepoxide, amphetamine and (Ca) were weak threshold-raisers. Arecoline, acetylcholine, methacoline and scopolamine were inactive. Unlike nicotine and phenothiazines, procaine threshold increase was transiently abolished by repetitive supramaximal stimulation. Doubling (Na) did not alter block by procaine or opipramol. Tubocurarine, a weak threshold-raiser, prevented repetitive firing during prolonged catelectrotonus. The two spikes showed differences in drug response, and were more sensitive than frog sciatic. Like frog sciatic, they tolerated wide variations in acidity and (Na) and showed prolonged duration, decrease of amplitude, and easily reversible block with urea above 1 M. Unlike frog sciatic nerve, they blocked with increased (K) without threshold lowering. Frog sciatic was also sensitive to phenothiazines and congeners, illustrating the nonspecificity of this drug group.

Chicago Medical School
Chicago, Illinois

276 Sanghvi, I., & Unna, Klaus R. Effect of muscarine on superior cervical ganglion of the cat. Federation Proceedings, 1963, 22, 214.

The superior cervical ganglion and its pre- and postganglionic fibers were exposed in anesthetized cats (chloralose-urethane). Administration of dl-muscarine (0.1-5.0 g) i.a. to the ganglion produced a contraction of the nictitating membrane, as measured with a force-displacement transducer. This effect was due to action on the ganglion and not on the nictitating membrane. Atropine and cocaine blocked the nictitating membrane contraction induced by muscarine whereas hexamethonium, in doses that caused a partial block of the response to the maximal preganglionic stimulation, failed to abolish the muscarine effect. Postganglionic potentials were recorded simultaneously with contractions of the nictitating membrane. Muscarine potentiated the contraction of the nictitating membrane and the postganglionic action potentials obtained on the tetanic (10/second) stimulation of the preganglionic nerve. Both S_1 and S_2 components of the postganglionic action potential were increased. As the intensity of the preganglionic stimulation was increased, the size of the contraction of the nictitating membrane was augmented parallel with the increase in S_2 as well as in the S_1 component of the postganglionic neurogram.

Department of Pharmacology
University of Illinois College of Medicine
Chicago, Illinois

277 Schwartz, M. A., Koechlin, B. A., & Krol, G. Metabolism of diazepam in rat, dog, and man. Federation Proceedings, 1963, 22, 367.

Diazepam labeled with tritium (H^3) in the 5-phenyl ring was given to rats, dogs, and two human subjects. After a 0.6 mg/kg i.p. dose, the rat excreted 22 percent of the H^3 in the urine and 57 percent in the feces. The dog, after 1 mg/kg i.v., excreted 60 percent of the dose in the urine (excretion rate half-life of 7 hours) and 35 percent in the feces. In man (10 mg diazepam p.o.) 70 percent of the dose appeared in the urine (excretion rate half-life of 3 days) and only 10 percent in the feces. The peak levels of blood H^3 in the 2 human subjects occurred in 2-4 hours and by thin layer chromatography was found to be almost exclusively labeled diazepam (0.08 and 0.06 /ml). Blood diazepam declined with a half-life of 7-10 hours followed by a slow component (half-life of 3 days) consisting of diazepam and its N-demethylated analog, 7-chloro-1, 3-dihydro-5-phenyl-2H-1, 4-benzodiazepin-2-1. The urinary radioactivity was associated with polar metabolites in each species. However, each species excreted different metabolites as determined by paper chromatography.

Hoffmann-La Roche, Inc.
Nutley, New Jersey

278 Speers, Louise, & Neeley, Arthur H. The synthesis, chemical and physical properties of Indoklon. Journal of Neuropsychiatry, 1963, 4, 153-156.

Indoklon (bis (2,2,2-trifluoroethyl) ether CF_3CH_2-O-CH_2-CF_3) tested in animals and clinically evaluated in animals and humans showed it to produce regular, dependable and powerful convulsions, which seem to make it useful in the treatment of mental illness. Indoklon is produced from trifluoroethanol, by the reaction of sodium trifluoroethoxide with trifluoroethyl p-toluenesulfonate. It is clear water-white, non-flammable liquid with a boiling point of 63.9° C. It is analytically proven to be greater than 99.9 percent pure and has extreme stability and chemical unreactivity.

Central Research Laboratories
Air Reduction Co., Inc.
Murray Hill, New Jersey

279 Stark, Paul, & Boyd, Eugene S. Effect of cholinergic drugs on hypothalamic self-stimulation response rates. Federation Proceedings, 1963, 22, 169.

The effects of the cholinergic agents, physostigmine and neostigmine, and the blocking agents, atropine and methyl atropine, on intracranial self-stimulation rates were studied. Dogs with chronically implanted electrodes were run on a continual reinforcement schedule at various current intensities. The administration of 1 cc of saline, 0.2 mg/kg of atropine, 0.2 mg/kg of methyl atropine, and 0.05 mg/kg of neostigmine had little or no effect on the response rates. The prior administration of atropine blocked the inhibitory action of physostigmine, whereas the prior administration of methyl atropine did not. The administration of 0.025 mg/kg of physostigmine did not affect the response rate when compared with the control.

Department of Pharmacology
University of Rochester
Rochester, New York

280 Stone, Clement A., Porter, Curt C., & Vernier, Vernon G. Some autonomic properties of amimethyline, a new antidepressant. Federation Proceedings, 1963, 22, 627. (Abstract)

Amimethyline (5-(3-methylaminopropyl)-5H-dibenzo (a,d) cycloheptene hydrochloride), possesses a number of interesting autonomic properties. The agent proved a potent antagonist of phenethylamine pressor responses, while potentiating those induced by levarterenol in the anesthetized, ganglic blocked dog. The new agent was the most active of several antidepressants (amitripty line, imipramine and their nor-analogs) studied. Extension of this finding to other levarterenol releasing agents demonstrated that the catecholamine depleting effects

of guanethidine, metaraminol, a-methyl-m-tyrosine, 6-hydroxydopamine, and tyramine on the hearts of mice were prevented by prior administration of amimethyline. Again this agent proved to be the most active of the several antidepressants examined. Amimethyline slightly inhibited the depleting effect of tetrabenazine on brain catecholamines in mice, although it completely antagonized its sedative action. Amimethyline, and several other antidepressants, were also found to be capable of preventing the adrenergic neuron-blocking action of guanethidine and bretylium on the cat nictitating membrane. The relationship of these several peripheral actions to central antidepressant actions of the compounds studied remains unknown.

Merck Institute for Therapeutic Research
West Point, Pennsylvania

281 Way W. L., & Costley, E. C. Neonatal study of meperidine-morphine sensitivity. Federation Proceedings, 1963, 22, 249.

Numerous clinical studies on adults indicate that in equianalgetic doses, morphine and meperidine produce a comparable degree of respiratory depression. The present work was undertaken because respiration of newborn rats appears to be depressed more by morphine than by meperidine. By means of the infant body plethysmograph, accurate measurements of tidal volume and respiratory rate were made in newborn infants and end-tidal carbon dioxide recorded with an infrared analyzer. With this apparatus carbon dioxide response curves were made before and after drug administration. The adult dose ratio of meperidine to morphine is considered to be 100 mg to 10 mg. The i.c. dose used for newborn infants was 0.05 mg/kg of morphine and 0.5 mg/kg of meperidine. Measurements were made on newborns aged 12-60 hours. Resting ventilation was decreased 22 percent with morphine and 8 percent with meperidine. The slope of carbon dioxide response curve was decreased 13 ml/mm PCO_2 with morphine and 8 ml/mm PCO_2 with meperidine. Morphine appears to produce a greater respiratory depressionthan meperidine, as measured by the carbon dioxide response curve.

Departments of Pharmacology and
Anesthesia
Cardiovascular Research Institute
University of California Medical Center
San Francisco 22, California

282 Weber, L. J., & Horita, A. Hydroxylation of L-tryptophan in situ by perfusion of rat intestine. Federation Proceedings, 1963, 22, 624.

Tryptophan is known to be a precursor for 5-HTP and 5-HT. The enzyme involved in the decarboxylation of 5-HTP has been investigated in some detail. The first step in 5-HT formation, that of hydroxylation, has not been studied extensively. The present experiments demonstrate a method whereby the hydroxylation of L-tryptophan can be shown in situ. The rats are pretreated with an MAO inhibitor, anesthetized with ether, and the gut cannulated and perfused with Tyrode's solution with or without L-tryptophan 3×10^{-3}M. A 20 percent increase of 5-HT over perfused control can be shown in the intestine after a 2-hour perfusion. A similar increase of 5-HT can be found in the brain. There is some depletion of 5-HT by perfusion with Tyrode's alone. 5-HT was measured by fluorimetric and biological assays. This method can be useful in the study of the hydroxylase system in situ.

Department of Pharmacology
University of Washington
Seattle, Washington

283 Weiss, L. R., Wolf, H. H., & Nelson, J. W. Interaction of drugs, stress and monoamine oxidase inhibition on hexobarbital induction times and body temperature. Federation Proceedings, 1963, 22, 626.

CNS drugs which generally lower body temperature and potentiate hypnotic sleep time may interact with stress and MAO inhibitors to modify these measurements. To clarify the relation between these effects, chlorpromazine, reserpine,

meprobamate, and phenobarbital in equipotent doses, were investigated under conditions of cold-restraint stress and MAO inhibition at peak action times. The changes in body temperature, hexobarbital induced ataxia, and loss of righting reflex times (LRR), were analyzed in rats. Stress produced emotional hypothermia and reduced ataxia and LRR. Similarly, iproniazid pretreatment alone, or with stress, lowered temperature and potentiated ataxia, and LRR. Each drug reduced ataxia and LRR equally while only chlorpromazine and reserpine produced hypothermia. Hypothermia, ataxia, and LRR were potentiated by combining stress and/or iproniazid with chlorpromazine, meprobamate and phenobarbital. These effects were reversed when reserpine was combined with stress and/or iproniazid. The effects of these drugs on body temperature and central depression appear to be through unrelated mechanisms. The changes produced by their interaction with stress and iproniazid seem to reflect primarily a general state of CNS inhibition or excitation.

College of Pharmacy
The Ohio State University
Columbus, Ohio

284 Westfall, T. C., & Watts, D. T. Catecholamine excretion in smokers and nonsmokers. Federation Proceedings, 1963, 22, 509. (Abstract)

The 24-hour urinary excretion of epinephrine determined fluorometrically in nonsmokers was found to be 6.48±0.82 μg/24 hours, whereas the excretion in smokers was 12.1± 0.87 μg/24 hours. There was no significant difference in the levarterenol output in smokers and nonsmokers. In other studies the excretion of epinephrine and levarterenol was determined at 30-minute intervals before, during, and after heavy smoking in 15 subjects. Epinephrine and total catecholamine output increases progressively above control levels during periods of heavy smoking. Experiments have also been carried out in which blood samples were obtained from the inferior vena cava (IVC) above and below the adrenals in patients undergoing cardiac catherization before, during, and following smoking 1 cigarette. The results show an increase in epinephrine levels of IVC from a control of 1.2 μg/l to a value of 3.7 μg/l during smoking.

Department of Pharmacology
West Virginia University Medical Center
Morgantown, West Virginia

285 Witoslawski, J. J., Campbell, E. H., & Hanson, H. M. Comparative study of four anorexigenic substances. Federation Proceedings, 1963, 22, 568. (Abstract)

Relative anorexigenic and behavioral potencies in rats were determined for dexamphetamine, as well as phenmetrazine and (-) 3,4-dichlor-α-methylphenethylamine hydrochloride (IV). Anorexic activity was determined by a simple 2-hour feeding test. Both learned and unlearned behaviors were measured. Random activity was measured by photocell activity cages; rats trained on an adjusting avoidance schedule gave a measure of learned behavior. Analysis of the data yielded the following values (mg/kg p.o.):

Compound	Anorexic ED_{50}	Rand. Act. ED_{200}	Operant Avoid. ED_{50}	Anorexia / Rand. Act.	Anorexia / Avoidance
d-Amphet.	0.99	0.82	0.48	1.21	2.06
Benzphet.	6.2	10	8	0.62	0.78
Phenmetr.	12.0	10	20	1.20	0.60
IV	1.15	12(?)	> 3	0.09(?)	< 0.38

Ratios of the two effects are shown in the fifth and sixth columns. It would appear that the presence of anorexigenic activity is not necessarily accompanied by measurable motor activity or lever pressing. Dexamphetamine and IV were also tested for anorexigenic effects in rhesus monkeys and dogs.

Merck Institute for Therapeutic Research
West Point, Pennsylvania

286 Zukauskas, E., & Machne, X. Chlorpromazine action on unit activity in the lateral hypothalamus. Federation Proceedings, 1963, 22, 625. (Abstract)

The spontaneous activity and the response of single hypothalamic units to brief (100 msec) repetitive stimulation of the midbrain reticular formation and of the lateral amygdala, were studied in unanesthetized paralyzed cats and in chlorpromazine-treated cats (1 mg/kg). A total of 102 units in the control group and 110 units of chlorpromazine-treated cats was studied; 39.6 percent of the control units and 43.6 percent of the units after chlorpromazine treatment responded to stimulation. Eight types of responses were identified according to the effects of stimulation (increase or decrease of firing rate with respect to the spontaneous rate) during and/or after the stimulus. The spontaneous firing rate was lower in chlorpromazine-treated animals. During stimulation chlorpromazine units behaved like the control units. During the poststimulatory period, fewer chlorpromazine-treated units than control units showed an increase in firing rate. The number of units which exhibited a decreased rate after the stimulus was much greater after chlorpromazine administration. In analogy to the posttetanic effects in other nervous structures, these findings suggest that chlorpromazine may interfere with the synaptic transmitter release mechanism.

Department of Pharmacology
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College of Medicine
Chicago, Illinois

287 Aghajanian, G. K. The effect of serotonin and norepinephrine on structural changes induced in brain microsomes. Federation Proceedings, 1963, 22, 450. (Abstract)

Ascorbic acid was found to induce in specially prepared rat-brain microsomes (membrane fragments) a gradual decrease of light scattering and protein fluorescence, phenomena that are taken to indicate the occurrence of structural changes. This effect of ascorbic acid was greatly accelerated by the addition of AMP or ATP. The influence of various neuropharmacologic agents on these induced structural alterations was studied in vitro (usual conditions: 0.05 M tris-chloride, pH 7.4, 0.1 mH ascorbic acid, and 2.5 mM AMP). 5-HT and levarterenol (norepinephrine) were found to be powerful inhibitors of these changes. In both cases there was complete inhibition at about 4×10^{-5}M, with graded lesser effects down to 5×10^{-6}M or lower. A number of other amines and amino acids, including acetylcholine, histamine, GABA, and 5-HTP were inactive under similar conditions. Among drugs studied it is of interest that chlorpromazine was a potent inhibitor, while phenobarbital had no effect. These studies suggest that membrane fragments (microsomes) from the brain are capable of undergoing changes in structure which can be induced by physiological substances (e.g., ascorbic acid and AMP) and that this process is modified by 5-HT, levarterenol, and certain other agents.

Yale University School of Medicine
New Haven, Connecticut

288 Maddison, David. The relation between recovery and plasma potassium levels in manic states. Medical Journal of Australia, 1963, 1, 173-174. (Letter)

A psychiatrist contests a statement from Dr. Cade's article (1962) on decreased plasma potassium levels in manic states. This article dogmatically asserts that manic states are biologically determined because lithium salts are an effective symptomatic treatment for manic excitement. This sort of sophistry is entirely at variance with the large body of knowledge which suggests that the efficacy of symptomatic treatment throws little or no light on causal factors. Such a gross

misconception is potentially dangerous.

Department of Psychiatry
University of Sydney
Sydney, Australia

289 Val'dman, A. V. Farmakologiya golovnogo mozga (afferentnyye puti, mezodientsefalicheskaya sistema, kora). (Pharmacology of the brain (afferent systems, mesodiencephalic system, cortex).) In: Val'dman, A. V. (Editor), Aktual'nyye problemy farmakologii retikulyarnoy formatsii i sinapticheskoy peredachi. Leningrad: I Leningradskiy Meditsinskiy Institut imeni Akademika I. P. Pavlova, 1963, 9-115.

The most important problem in modern pharmacology of the nervous system, i.e., the effect of neurotropic drugs on individual structure and functional systems of the brain, was studied by comparing the data on the effect of inhibiting and stimulating drugs on specific and diffuse afferent systems, reticular formation, medial thalamic systems, as well as some intracortical processes. The following agents were reviewed: narcotic, analgesic, sympathomimetic, and cholinergic drugs, chlorpromazine, reserpine, serotonin, and stimulants. The experiments on unnarcotized animals indicated that the inhibiting effect of narcotic drugs varied, depending on the type and dose of narcotic drugs used. The inhibiting effect of barbiturates was most specific. In immobilized cats, analgesics had no effect on the conduction in specific afferent systems. The effect of analgesics on the activation of cerebral cortex in unnarcotized rabbits varied. The experimental studies providing the quantitative data on a relatively high content of sympathomimetic amines in some subcortical structures indicated the importance of catecholamines and pathological activity of the brain; however, these studies were not adequate to indicate that the observed effects of pharmacological agents were actually the result of their effect on adrenoactive systems. Extensive experimental studies on animals indicated that chlorpromazine reduced the number of high frequency waves in the EEG. Chlorpromazine, even in large doses, did not change the level of serotonin, noradrenaline and dopamine, and it also had no substantial effect on enzymes participating in the catalysis of monoamines. Chlorpromazine prevented an increase of serotonin level in the brain after administration of 5-hydroxytryptophan. Studies on animals indicated that the effect of reserpine on bioelectrical phenomena of the brain was less pronounced than the effect of chlorpromazine. Intravenous administration of reserpine to monkeys evoked general relaxation and eliminated aggressiveness. Reserpine also had a sedative and relaxing effect on human beings. It released serotonin from different tissues; the largest quantity of serotonin was released from the brain stem as compared with other sections of the brain. Excitation and sympathomimetic effects evoked by LSD were suppressed by reserpine as well as chlorpromazine. The experimental data indicated that acetycholine, anticholinesterase, and atropine-like drugs evoked a pronounced effect on the conduction of afferent impulses in the brain, on the EEG, and physiological reactions connected with the reticular formation and thalamic systems. The convulsive effect of stimulants and their antagonism with narcotics were studied extensively. In a proposed electrophysiological classification of stimulants of the CNS the authors explained the excitatory effects of the drugs on bioelectrical manifestations in the brain.

(No address)

290 Rathbun, R. C. & Slater, I. H. Amitriptyline and nortriptyline as antagonists of central and peripheral cholinergic activation. Psychopharmacologia, 1963, 4, 114-125.

The purpose of this study was to compare the relative potency of amitriptyline and nortriptyline as peripheral anticholinergic agents and to determine whether compounds of this type modify central nervous system phenomena that might be considered as cholinergic in origin. The activity of both drugs were compared on guinea pig ileum and salivation of dogs. Both were active anticholingeric agents, though somewhat atypical. Amitriptyline caused suppression of salivation at lower doses than nortriptyline. On guinea pig ileum, it was about twice as active as nortriptyline. Both compounds decreased the tremor and salivation induced in mice by Tremorine and differed from atropine in showing greater effect on tremor than upon salivation. Both drugs were effective in elevating the threshold dose of arecoline that produces desynchronization of the high voltage slow activity with spindles seen in the EEG of cats with lesions at the pontomesencephalic junction. They did not cause EEG behavioral dissociation like atropine. It is suggested that although these compounds are effective in antagonizing the central effects of cholinergic agents, they are different in this regard from atropine and other tertiary amines that have been reported to cause hallucinations in patients. That dryness of the mouth as a side effect occurs with both drugs is not considered surprising even though they are less active than atropine, since the clinically recommended dose (25 mg 3 or 4 times a day) is much higher than the usual dose of atropine. (1 Refs.)

Department of Neuropharmacology
Lilly Research Laboratories
Eli Lilly & Company
Indianapolis 6, Indiana

291 Sandler, M., Ruthven, C. R. J., Contractor, S. F., Wood, Carl, Booth, R. T., & Pinkerton, J. H. M. Transmission of noradenaline across the human placenta. Nature, 1963, 197, 598.

Fetal bradycardia following i.v. noradenaline (racemic DL mixture) injection into the mother may be due, in part at least, to a direct action of noradenaline on the fetal circulatory system. Following i.v. injection of ^{14}C-DL-noradenaline into the mother, radioisotopically labeled noradenaline content of serum deriving from maternal venous, umbilical venous (afferent), and fetal heart blood was measured. Appreciable amounts of NE crossed the placenta to appear in blood flowing from the placenta to the fetus. During this blood passage through the fetus, all NE had disappeared from the circulation, possibly by both tissue binding and metabolic change. Though it is likely that the inactive D- and the physiologically active L-isomers are metabolized in the same way, no information is available so far of the preferential transfer of either across biological membranes. (4 Refs.)

Bernhard Baron Memorial Research Laboratories
London England

292 Bergen, John R., Czicman, John S., & Koella, Werner P. Influence of a plasma protein fraction from schizophrenic and normal persons upon the optic evoked responce in the rabbit. Journal of Neuropsychiatry, 1963, 4, 219-223.

This report describes the effect of plasma fractions from schizophrenic patients and from normal subjects upon the conductile properties of the rabbit's optic pathways. Optical potentials in rabbits with chronically implanted electrodes were analyzed by measuring peak-to-peak amplitude between the positive and negative component of the

primary response to light stimulation as well as by measuring the latency of the positive peak. The plasma fraction from schizophrenics produced a short-lived reduction in amplitude and a slight shortening of the latency of the evoked response. Furthermore, these samples induced a marked reduction of the variability of amplitude and latency. Samples from normals induced a nonsignificant decrease of latency and no significant change in amplitude or variabilities. The results are related to earlier comparisons of the actions of LSD-25, mescaline, and schizophrenics' plasma globulin precipitate, wherein different effects were found on amplitude and latency, but they produce an identical effect on intrinsic modulation of the response: a decrease in its variability.

Laboratory of Neurophysiology and Neuropharmacology
Worcester Foundation for Experimental Biology
Shrewsbury, Massachusetts

293 Friedman, Alexander H. Norepinephrine depletion in the brainstem by Tremorine. Federation Proceedings, 1963, 22, 272.

The tremor and rigidity produced by Tremorine (20 mg/kg i.p.) in the rat, mouse, and guinea pig are accompanied by significant decreases in the levels of levarterenol (norepinephrine) found in brainstems. The general pattern consists of a fall followed by restoration to control levels. The time course of these biochemical changes approximates that of the tremor and rigidity. A maximal decrease of 25 percent is obtained in the rat in 1 hour, of 16 percent in the mouse in 5 minutes, and of 28 percent in the guinea pig at an intermediate time interval. Similar statistically significant decreases occur in the cerebral and cerebellar cortices in the rat and guinea pig. However, in the mouse, the fall in the brainstem is accompanied by a rise in the cortex. The effect in the brainstem is most pronounced in laboratory-adapted animals and may be reversed in excited animals.

Department of Pharmacology
University of Wisconsin Medical School
Madison 6, Wisconsin

294 Fishman, Vivian & Goldenberg, Harry. Metabolism of chlorpromazine. IV. Identification of 7-hydroxychlorpromazine and its sulfoxide and desmethyl derivatives. Proceedings of the Society for Experimental Biology and Medicine, 1963, 112, 501-506.

This study investigates whether the clinical reaction to chlorpromazine bears any relation to the pattern of its metabolism and the subsequent disposition of its metabolites. Four phenolic metabolites of chlorpromazine (polar fraction) were isolated from dog and human urine and identified. Human subjects were given daily doses of 300-1,200 mg chlorpromazine HCl. Female mongrel dogs were fed chlorpromazine HCl or promazine HCl, 4 mg/kg b.i.d. Urine was collected during preliminary control period and during medication. Metabolites were isolated by solvent extraction and paper chromatography. They were submitted to methylation, oxidation, or reduction and then identified as 7-hydrochlorpromazine, 7-hydroxychlorpromazine sulfoxide, 7-hydroxy-nor$_1$chlorpromazine, and 7-hydroxy-nor$_2$chlorpromazine. These four 7-hydroxychlorpromazines constitute eight metabolites in urine since they are excreted both in free form and as glucuronic acid conjugates. When they are combined with the five nonphenolic metabolites present in the nonpolar fraction, they add up to 13, besides the additional hydroxy derivatives. Hydroxylation and gluceronide formation are species dependent. They seem to be the more important biotransformation pathways in humans compared to dogs. (13 Refs.)

Department of Biochemistry
Hillside Hospital
Glen Oaks, New York

295 Fujita, Shigeo & Rosenzweig, Norman. Use of the cortical epinephrine pressor response in rabbits as a diagnostic test for schizophrenia. Psychopharmacologia, 1963, 4, 367-376.

Epinephrine topically applied to the cerebral cortex of rabbits after injection with serum from schizophrenic patients showed that the cortical epinephrine pressor response is not a reliable clinical tool for diagnosing schizophrenia. Initial tests with 113 rabbits showed that one-third of them died from the i.v. injection of serum from 15 schizophrenic male patients. Injected rabbits which survived, as well as control animals, gave badly mixed responses on the first as well as the following tests. On completion of the tests, 15 rabbits were tested with serum from eleven normal subjects. They gave "schizophrenic patterns" half the time. When serum was injected into rabbits "acutely," after completion of surgery to expose the cortex rather than a day earlier, the pressor response to epinephrine was somewhat higher both for serum from schizophrenics as from normal subjects. Chlorpromazine seemed to prevent pressor response, but iproniazid did not. Reserpine showed pressor responses and sensitization to topically applied epinephrine in every case. Though the results on tests with hundreds of rabbits over more than a year did not justify further study, some positive findings have emerged. Human serum contains substances toxic to rabbits, with some indication that schizophrenic serum has greater toxicity than non-schizophrenic serum. It was also shown that local application of 5 percent epinephrine solution to the cerebral cortex of rabbits causes rise in blood pressure in half of the test animals treated with normal serum. (24 Refs.)

University of Michigan
Ann Arbor, Michigan

296 Kopin, I. J. & Gordon, E. Metabolism of drug-released norepinephrine-H^3. Federation Proceedings, 1963, 22, 389. (Abstract)

A portion of administered levarterenol (norepinephrine-H^3) is bound in the tissues and slowly released. Drugs which deplete tissues of their levarterenol content cause an increased rate of isotope excretion. Examination of the increases in the excretion of levarterenol and its deaminated and O-methylated derivatives gives information regarding the metabolic fate of the levarterenol-H^3 depleted from the stores. After tyramine (T), DMPP, and acetylcholine, the percentage increases in levarterenol and normetanephrine (NM) exceeds the increase in total radioactivity excretion; i.e., release of free levarterenol into the circulation. After reserpine (R), the increase in deaminated catechols is greatest, indicating destruction within the nerve. Guanethidine and alpha methyl DOPA, like R, deplete tissues of their levarterenol content by destruction by MAO before activation of the catecholamine, but have some T-like effects in releasing free levarterenol as well. After pretreatment with an MAO inhibitor R-like compounds have a T-like effect.

National Institutes of Health
Bethesda 14, Maryland

297 Kravitz, E. A., Kuffler, S. W., & Potter, D. D. The selective localization of gamma-aminobutyric acid (GABA) in isolated inhibitory axons of lobsters. Federation Proceedings, 1963, 22, 220. (Abstract)

Since GABA imitates the actions of the neurally released inhibitory transmitter in Crustacea, it was of interest to establish its occurrence and localization in these animals. Ten substances that block neuromuscular transmission in crayfish have been extracted from the crustacean central and peripheral nervous systems and the analyses have been extended to single isolated axons. Long stretches of inhibitory and motor fibers in the leg of

the lobster have been removed and separated. GABA was concentrated in the inhibitory axon (about 0.5% wet weight) while in the accompanying motor fiber no GABA was detected. GABA was determined enzymically (assay of Jakoby and Scott) and, if present in motor fibers, it could not have been more than about 1/1000 of the concentration in inhibitory axons, when most sensitive assay was used. The other blocking compounds were found in both neuron types. Glutamate, the only identified excitatory compound, occurs in motor and inhibitory fibers. GABA may have a function specifically related to inhibitory neurons in Crustacea.

Harvard Medical School
Boston, Massachusetts

298 Leonards, Jack R. Aspirin and gastrointestinal blood loss. Federation Proceedings, 1963, 22, 369. (Abstract)

The red blood cells of 8 normal humans were labeled with Cr^{51} and the amount of blood loss was determined by counting the isotope in a homogenized aliquot of stool. Blood loss in each subject was measured during 3 randomized collection periods of 8 days each: 1) control; 2) tablets of acetysalicylic acid (aspirin), 2.5 g/day, and 3) the equivalent amount of drug taken as a solution of calcium acetysalictylate. Blood loss in ml/day (average SE) was control 0.6 ± 0.6, acetysalicylic acid tablets 3.9 ± 0.9, and calcium acetylsalicylate 2.2 ± 0.3. As previous work has shown that an effervescent solution of sodium acetylsalicylate buffered with sodium citrate does not cause bleeding, it is concluded that buffering the acidity of the stomach is an important factor in the prevention of gastrointestinal bleeding associated with acetylsalicylic acid ingestion.

Western Reserve University
Cleveland, Ohio

299 Libow, L. S. & Durell, J. Interrelationships between regulation of thyroid gland function and psychosis. Federation Proceedings, 1963, 22, 510. (Abstract)

Study of 2 patients with different psychotic manifestations has provided evidence appearing to corroborate the existence of a significant interaction between the regulation of thyroid gland activity and the CNS mechanisms of psychosis. One patient, a chronic schizophrenic, showed a periodic transition between a hyperactive behavioral phase and a mute, retarded phase. Serial measurements of I^{131} uptake provides evidence that abrupt changes in thyroid gland regulation accompanied his behavioral transitions. In the second patient, the opportunity for another approach presented itself. She was hypothyroid (not myxedematous) and alterations in the severity of psychosis appeared to follow experimental manipulation of thyroid regulatory mechanisms. Most striking was the coupled increase in TSH secretion and exacerbation of psychosis which occurred immediately upon cessation of triiodothyronine therapy. Interaction between the mechanisms of psychosis and thyroid gland regulation probably occurs in the brainstem.

National Institutes of Health
Bethesda, Maryland

300 Ling, Alfred S. C. The effect of Indoklon on brain metabolism. Journal of Neuropsychiatry, 1963, 4, 161-163.

The experimental studies of Indoklon-induced on brain metabolism indicate significant increase in brain cholinesterase activity as well as marked diminution in brain potassium with increased brain sodium and serum potassium. Investigations were made on various aspects of brain metabolic activity following exposure of animals to convulsive doses of Indoklon. These studies

were concerned with (1) brain oxidasive metabolism in vitro, (2) brain cholinesterase activity in vitro and in vivo, and (3) brain electrolyte and water distribution. The results of the studies of Indoklon-induced convulsions on brain metabolism in rats indicated (1) a significant increase in brain cholinesterase activity, (2) a marked diminution in brain potassium with increased brain sodium and serum potassium, and (3) no significant effect on the brain oxidative metabolism carbohydrate substrates or water distribution.

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Baltimore, Maryland

301 Kohl, H., Brune, G., Steiner, W., & Himwich, H. The dimethylamine configuration in chlorpromazine. Federation Proceedings, 1963, 22, 568. (Abstract)

The frequent occurrence of an N,N-dimethylamine configuration in psychotropic substances prompted this study of its significance in chlorpromazine (CP). The pharmacological effectiveness of CP, desmonomethyl chlorpromazine (Nor_1CP), desdimethyl chlorpromazine (Nor_2CP), and chlorpromazine sulfoxide (CPS) were compared by relating the degree of behavioral depression evaluated by 6 behavioral tests) to brain phenothiazine levels determined by chemical assay when equimolar dosage levels ranging from 0.0422-0.1266 m M/kg were injected i.p. in rats. In addition the relative potencies in raising thresholds for maximal EEG recruitment and blocking of EEG alerting response to pain were studied in rabbits injected i.v. Progressive demethylation of chlorpromazine was associated with a pronounced loss of pharmacological potency. The Nor_1CP accumulated in the brain more readily than the other derivatives. When the amounts in the brain were related to the degree of depression, chlorpromazine was clearly the strongest agent. It was 3 times as potent as Nor_1CP and at least 4 times as potent as Nor_2CP. CPS showed no behavioral depressant activity. Neurophysiological findings were consistent with behavioral results.

(No Address)

302 Redick, Thomas F., Renfrew, Alice G., Pieri, Lorenezo, & Marrazzi, Amedeo S. Attempt to separate by electrodialysis a cerebrally active small moiety from "taraxein-like" blood fractions. Federation Proceedings, 1963, 22, 569. (Abstract)

Efforts to separate by electrodialysis an active small moiety from its polypeptide carrier prepared by Heath and Leach procedures or by curtain electrophoresis of Frohman and Gottlieb are reported. Initial findings include: serotonin, a known small molecule of high cerebral synaptic inhibitory potency, is electrodialyzable without denaturation; i.e., retains cerebral synaptic inhibition; serotonin is accumulated in the cathode chamber during electrodialysis of a model serotonin albumin system.

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Pittsburgh, Pennsylvania

303 Fenster, Eric & Towne, Jack C. Solubilization of serotonin by rat brain extracts in lipid solvents. Federation Proceedings, 1963, 22, 624.

The findings that 5-HT (serotonin) can complex with lipids and the use of petroleum ether (PE) to remove lipids from tissue extracts prepared for bioassay of 5-HT suggest study of acetone (A)-PE extraction procedures to determine the nature of "lipid-receptors" and the fate of 5-HT during the preparation of samples for bioassay. 5-HT in A and PE extracts was analyzed (1961). PE and water are added to dried A extracts and each phase analyzed

for 5-HT. At least 75 percent of 5-HT is found in the PE fraction compared to 2 percent in the same fraction in the absence of tissue. Several lipids, including phosphatidic acid, give a similar result. Response of 5-HT in brain tissue to reserpine and MAO inhibitors is also demonstrated in PE fractions of extracts of treated animals. Direct extraction of tissues with PE shows no 5-HT but demonstrates the ability of extract substances which can solubilize 5-HT in PE. Residue from direct PE extraction contains 5-HT. The lipid-5-HT complex does not occur in vivo, and the specificity of bioassay using A and PE must be reevaluated.

Radioisotope Service
VA Research Hospital
Chicago, Illinois

304 Tyce, Gertrude M., Flock, Eunice V., & Owen, Charles A., Jr. 5-hydroxyindoles in the rat after hepatectomy. Federation Proceedings, 1963, 22, 632. (Abstract)

A deficiency in the brain of 5-HT has been suggested in hepatic coma. Previous work in this laboratory has shown that slight increases in the concentration of 5-HT occurred in the brain of the dog in coma following complete hepatectomy. A study has been made of changes in the concentration of 5-HT and 5HIAA in the brains of rats after hepatectomy. The concentration of brain 5-HT showed a 2-fold, and that of 5HIAA a 3-fold increase, 24 hours after hepatectomy, indicating a rapid turnover of 5-HT. In an attempt to determine the source of the increased amounts of 5-hydroxyindoles found after hepatectomy, the concentration of the aromatic amino acids tryptophan and tyrosine was measured in plasma, brain, and skeletal and heart muscle. The 4- to 5-fold increases in the concentration of tryptophan and tyrosine were found in the brain of the rat after hepatectomy; however, the concentrations in the brain were never as high as those found in plasma, cardiac, or skeletal muscle. Fluorometric methods were used to measure 5-hydroxyindoles, tryptophan, and tyrosine.

Mayo Clinic & Mayo Foundation
Rochester, Minnesota

305 Cohen, Gerald, & Hochstein, Paul. Enzymatic mechanisms of drug sensitivity in brain. Diseases of the Nervous System, Monograph Supplement, 1963, 24, 1-4.

Central nervous system tissue is predisposed to oxidative damage in the presence of peroxide-generating drugs due to the absence of adequate mechanisms for detoxifying hydrogen peroxide. The purpose of the study was to show that dihydric phenols and related quinones, which are compounds of benzenoid structure and are potent inhibitors of brain glycolysis in vitro, should be regarded as potential poison to the CNS in vivo. Initial studies on the inhibitory effects of this group of compounds on aerobic glycolysis in the brain led to hydrogen peroxide as a common toxic intermediate. Hydrogen peroxide, known as a powerful oxidizing agent, would react with and oxidize cellular constituents such as they enzyme G-3-PD (glyceraldehyde-3-phosphate dehydrogenase). Glutathione peroxidase, linked to glucose metabolism, has been established as a major cellular pathway of peroxide detoxication, but this important protective enzyme was found absent in the brain. To explain the absence of this protective factor, the authors have elucidated the biochemical etiology of drug-induced hemolysis as a disorder of hydrogen peroxide intoxication. (18 Refs.)

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New York State Psychiatric Institute
New York, New York

306 Belenkov, N. Yu. & Chirkov, V. D. O vliyanii vozbuzhdeniya korkovykh

proyektsionnykh zon na protsessy generalizatsii eletrichoskoy reaktsii (desinkhronizatsii) v kore bol'shikh polushariy goloynogo mozga. (Effect of excitation of cortical projection areas in the processes of generalization of electrical reaction (desynchronization) in the cerebral cortex.) Zhurnal Vysshey Nervnoy Deyatel'nosti imeni I. P. Pavlova, 1963, 13, 390-397. (Russian)

On the basis of brain transection and use of chlorpromazine, it was determined that when sound or photic stimuli were applied to animals, the generalization of desynchronization in the cerebral cortex depended not only on excitation in an ascending path of the reticular formation, but also on excitation in the corresponding projection area from which it irradiated into the entire cortex. In all experiments the greater the distance from the projection area, the lower the irradiation of excitation. The majority of the experiments were carried out on 94 unnarcotized adult female cats immobilized with 0.2. mg/kg of procurane. In some experiments, 0.8-0.9 mg/kg of 10% Hexenal solution and 1.0 g/kg of urethan were used for mild narcosis. The body temperature of animals was maintained at 37-39° C. Photic (50 flashes per second) and sound (a tone of 80 cycles) stimuli were used to evoke the reaction of desynchronization of electric activity of the brain. Biopotentials were recorded by means of silver chlorinated electrodes; the lead was monopolar. In the first series of the experiments after an initial recording of the EEG and its changes to a light or sound stimuli, a vertical cortical transection was performed separating the corresponding projection area from the cerebral cortex. Some 30-40 minutes later when the excitation of the cerebral cortex cells was restored, the EEG was recorded again either with sound or light stimulus. In 25 out of 41 experiments, desynchronization was reduced outside the projection area and remained almost unchanged in the projection area. In the second series, an i.v. administration of chlorpromazine (2.5-7 mg/kg) inhibited the cortical desynchronization without transection; in 14 out of 22 experiments, desynchronization was uniformly reduced in the projection area as well as other areas of the cortex. In the third series after the projection area had been isolated by transection, 2.5-7 mg/kg of chlorpromazine were administered i.v.; in 22 out of 26 experiments, somewhat reduced desynchronization remained in the projection area only. In 4 experiments of the third series, desynchronization outside the projection area did not disappear completely, although it was sharply reduced.

Chair of Normal Physiology of the Gor'kiy Medical Institute

307 Ling, George M. EEG effects of some biogenic amines and psychoactive drugs. Journal of Neuropsychiatry, 1963, 4, 255-264.

The effect of biogenic amines on four basic types of EEG patterns in unanesthetized deafferented cats are presented with data on blockage by some psychoactive drugs. Surgical procedures previously described were used to provide somatic deafferentation. Rothballer's A, B, C, and D patterns were employed in judging degree of activation. The degree of activation produced by injected norepinephrine, isoproterenol, histamine, acetylcholine, serotonin, DOPA, and dopamine are presented. The EEG deactivating effects of the psychoactive drugs chlorpromazine, amitriptyline, and tranylcypromine are indicated.

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308 Lukshina, N. I. The effect of Benactyzine on the activity of monoamine

oxidase in the brain and liver of the cat. Federation Proceedings, 1963, 22, 252-254.

Benactyzine injections in vivo decreased MAO activity in the diencephalon and the liver of the cat, while it increased in the visual cortex. In vitro Benactyzine inhibited the diencephalon MAO as well as that in the visual cortex. Benactyzine, diethylaminoethyl of benzoic acid, was injected i.m. in doses of 10 mg/kg. Animals were sacrificed and tissue homogenates were prepared. Results showed the following: (1) Two hours after injection of Benactyzine MAO activity decreased an average of 21 percent in the diencephalon, 19 percent in the liver, while it increased by 20 percent in the visual cortex as compared to controls. (2) MAO activity remained unchanged in the diencephalon 1 day after single injection and 1 day after the last of three injections of Benactyzine. (3) In vitro, in a concentration of $4x10^{-4}$M, MAO activity was decreased by an average of 15 percent in the diencephalon and 11 percent in the visual cortex. At a concentration of $4x10^{-3}$M, the decreases were 41 and 40 percent, respectively. All differences were found statistically significant. (23 Refs.)

Institute of Toxicology
USSR Ministry of Health
Leningrad, USSR

309 McAuliff, J. P., Rosenberg, F. J., Arnold A., Harris, L. S., & Archer, S. Tissue norepinephrine and serotonin levels following graded amounts of 1-[2-(5, 6-dimethoxy-2-methylindolyl-3) ethyl] -4-phenylpiperazine (oxypertine). Federation Proceedings, 1963, 22, 567.

Oxypertine potentiates hexobarbital, is anticonvulsant vs. pentetrazol, depresses spontaneous activity, and causes taming in rhesus monkeys. It is also adrenolytic and antihistaminic. Tissue levels of levarterenol 5-HT were followed in rats given 2.5, 10, or 40 mg/kg oxypertine s.c. Pooled tissue from groups of 7 or 8 rats each was homogenized, extracted from NaCl-saturated butanol and the solvent phase extracted with dilute acid (Shore Olin procedure). In this extract, 5-HT was estimated. Separate aliquots of the extract were oxidized with ferrocyanide and fluorescence was developed by the Von Euler-Lishajko procedure for levarterenol estimation. This combination proved more consistent for levarterenol in our hands than either procedure alone. One hour after s.c. medication, levarterenol tissue levels were reduced following 10 or 40 mg/kg, but not after 2.5 mg/kg. The 5-HT levels were not affected. Oxypertine is unique in that it can deplete catecholamines for short periods of time without affecting 5-HT levels.

Sterling-Winthrop Research Institute
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310 McCaman, R. E. Microdetermination of choline acetylase and its distribution in nervous tissue. Federation Proceedings, 1963, 22, 170.

A sensitive method was developed for the quantitative determination of choline acetylase in µg quantities of nervous tissue. The incubation conditions are 0.07M potassium phosphate buffer (p^H 7.5); choline chloride, 25 mM; magnesium developed for the quantitative determination of choline acetylase in µg quantities of nervous tissue. The incubation conditions are 0.07M potassium phosphate buffer (p^H 7.5); choline chloride, 25 mM; magnesium sulfate, 20 mM; eserine sulfate, 0.1 mM; C 14-acetylcoenzyme A, 3 x 10-5M. Tissue samples weighed 0.5 to 20 µg dry weight. A reineckate precipitate (choline plus enzymatically formed C 14-acetyl choline) was collected by centrifugation, and radioactivity determined in a scintillometer. The method is capable of detecting 1 x 10-13 M of enzymatically formed C 14-acetylcholine. Preliminary results on the distribution of the enzyme in a few representative samples of rabbit nervous tissue are as follows: (the units of activity are µM product/gram dry weight and hour) cerebellum 0.5 (molecular), 1.5 (granular), 0.6 (subjacent white matter); dorsal root ganglion 1.5; caudate 4.0; cortex 8.5 (molecular), 8.5 (neuronal layers), 2.5 (subjacent white matter); dorsal root ganglion 1.5; caudate 4.0; cortex 8.5

(molecular), 8.5 (neuronal layers), 2.5 (subjacent white matter); spinal cord 0.5 (dorsal and lateral columns), 4.0 (dorsal horn), 25 (ventral horn). Variations of over 100-fold have been observed for the activities in different fiber tracts.

Institute of Psychiatric Research
Indiana University
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311 McGeer, P. L., McGeer, E. G., & Wada, J. A. Central aromatic amine levels and behavior. II. Serotonin and catecholamine levels in various cat brain areas following administration of psychoactive drugs or amine precursors. Archives of Neurology, 1963, 9, 81-89.

Measurement of serotonin, norepinephrine, and dopamine in 16 brain areas of cats treated with psychoactive drugs or amine precursors in doses shown to have definite effects in a behavioral situation are reported. Cats had previously been studied with respect to conditioned avoidance behavior as influenced by psychoactive drugs and amine precursors. Amine levels were determined following administration of behavioral-effective doses. Details of dissection and analysis are given. Average concentrations of amine in normal cat brains and ratios of amine level in experimental cats to the average in control cats are tabled for 12 drug conditions. Effective dosage information is provided. Results are discussed in terms of comparison with control animals and prior behavioral data.

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312 Monroe, Russell R., Balis, George U., & Ebersberger, Ethel. The hypnotic effects of alpha and beta chloralose in rats. Current Therapeutic Research, 1963, 5, 141-153.

Dose-effect regression curves for CNS effect of alpha and beta chloralose were determined in rats. Progressive hypnotic, sedative, and anesthetic effects were caused by both chloraloses. Hyperexcitability at various stages may be a manifestation of depressed central inhibitory tone rather than a subconvulsive state of cortical neurons. The findings reported here show that alpha chloraloses elevate convulsive threshold in rats and therefore seems to suggest that glucochloraloses are true CNS depressants. They demonstrate a consistent progression depending on dose levels from light sedation to deep coma. Two effects were unusual for CNS depressants. The first was that at the stage of maximal ataxia spontaneous myoclonic jerks were observed. The second was a generalized clonic response during anesthesia. The hypothesis is suggested that hyperexcitability under chloralose sedation may reflect a temporally and spatially different depressant action which removes central inhibitory mechanisms. It had been claimed in a previous study that the effect on the CNS depends on the dose. A dose of 2 to 10 mg/kg chloralose increases the amplitude and lowers the threshold of the recruiting response and at the same time increases the sensory cortical response. At anesthetic doses, alpha chloralose depressed the reticular system and reduced potentials evoked at both the reticular and cortical levels. (37 Refs.)

Psychiatric Institute
University of Maryland
Baltimore, Maryland

313 Broer, Henry H., Cates, Norman, & Sankar, D. V. Siva. Effect of d-lysergic acid diethylamide on oxygen uptake and norepinephrine levels. Federation Proceedings, 1963, 22, 626 (Abstract)

Oxygen consumption in the rat is increased by LSD while chlorpromazine depresses it, and BOL had very little effect. LSD increased the incorporation of radioactivity

into different visceral and brain tissue of the rabbit injected i.v. with labeled 5-HPT or histidine or levarterenol (norepinephrine). These results suggest increased metabolic rate under the influence of LSD. Further, rabbits were given i.v. levarterenol-7-C^{14} follow 45 minutes later with 500 μg of LSD or saline (controls). Radioactivity in the liver, lung, kidney, spleen, heart, cerebrum, cerebellum, stem, and the rest of the brain was assayed using a liquid scintillometer. The total radioactivity increased in all the tissues except in the kidney in the LSD-treated animals. However, most of the increase was in the fraction containing the acidic metabolites of levarterenol. The levels of levarterenol were lower in the LSD group in all the tissues except in the spleen. LSD probably releases levarterenol which is then further metabolized giving rise to lower tissue levels. This is in contrast to the effects of LSD on 5-HT (increased levels and binding) and on histamine (decreased levels and increased binding).

Creedmoor State Hospital
Jamaica 27, New York

314 British Medical Journal. Blurred signposts in schizophrenia. British Medical Journal, 1963, 5332, 695-696. (Editorial)

Research on the biochemistry of schizophrenia from 1956-1961, about 1,700 papers, has yielded the following postulates: taraxein, an allegedly toxic euglobulin, is present in the plasma of schizophrenics; serum gammaglobulins and macroglobulins are increased; an increase occurs in urinary indoles which is not attributable to exogenous factors; and hyperaminochromia ensues whereby the urine contains excess chromogenic substances. Work intended to establish a correlation between decreased CSF levels of neuraminic acid and schizophrenia has yet to be corroborated. The Russians have concentrated on endeavoring to detect an infectious origin for schizophrenia. A symposium at the New York Academy of Sciences (1962) exemplified the current emphasis being placed on the isolation of protein and other fractions from the serum of schizophrenics which induce behavioral modifications when injected into animals. (10 Refs.)

British Medical Association
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315 Mirsky, I. Arthur. Symposium on psychoendocrinology. V. Peptides as neurohormones. Canadian Psychiatric Association Journal, 1963, 8, 41-45.

The role of hormones in CNS regulation is reviewed, with emphasis on neurohypophyseal peptides. Although little is known concerning the precise nature and function of the various peptides which can be isolated from the hypothalamico-neurohypophyseal system, these probably result from the hydrolytic action of some proteolytic enzyme. Angiotensin I and II, pepsitensin, pepsanurin, and nonpeptide bradykinin are noted. Aside from their postulated role in the activation of the anterior pituitary gland and their known action on peripheral mechanisms, the hypothalamic neurohormones may play a role in the activation of neuronal centers in the hypothalamus. The presence of an active polypeptide, substance P, in appreciable concentrations in the brain suggests that the active peptides may exert some regulatory activity on some other portions of the CNS. For example, angiotensin II exerts an effect on higher brain centers supporting the concept that centrally produced peptides may represent a class of neurohormones whose potential is still to be evaluated.

Department of Clinical Science
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316 Hernandez-Peon, R. & Chavez-Ibarra, G. Limbic Cholinergic and adrenergic pathways mediating sleep and alertness. Federation Proceedings, 1963, 22, 638. (Abstract)

Localized chemical stimulation with minute crystals of acetylcholine and levarterenol was tested in cats with cannulas implanted in the brain. Acetylcholine in the region of the medial forebrain bundle (from medial preoptic to posteromedial hypothalmus) elicited behavioral and EEG manifestations of sleep. Sleep often reached the "desynchronized stage," after passing through a "synchronized stage." Acetylcholine in midbrain tegmentum produced alertness and motor hyperactivity and in the red nucleus, catatonic like postures. Carbachol in septal areas elicited rage behavior and a state of "magnetic attention" in which the animal's gaze followed any moving insignificant object for long periods, as an iron follows a magnet. Levarterenol in the medial preoptic region produced alertness and motor excitation. Autonomic effects were also obtained. Results suggested a cholinergic hypnogenic pathway in medial forebrain bundle, a cholinergic attention-controlling pathway in septum and an adrenergic arousing pathway in preoptic region.

Unidad de Investigaciones Cerebrales
S. S. A., Mexico City D.F., Mexico

317 Kita, T., Kamiya, H., & Kiyota, C. Effect of intraventricular injection N-methylated GABA-derivatives on the central nervous system of conscious mice. Biochemical Pharmacology, 1963, 12, 213-221.

N-methylaspartic acid is one of the most active substances existing naturally in the brain, possibly functioning as an excitatory neurochemical transmitter. Recent studies with GABA and related compounds have shown them to significantly influence behavior patterns in animals. Much of the activity of these compounds is influenced by their chemical structure; i.e., the number of carbon aliphatic chains between the anionic and cationic sites and their sterioconfiguration. In this study, various amino-acids were tested. The N-methyl derivatives of aspartic and glutamic acids gave striking results, particularly N-methyl-DL-aspartic acid monohydrate, N-methyl-D-aspartic acid and N-methyl-DL-glutamic acid all of which induced convulsions on mice after intraventricular injection of amounts ranging from 0.1 μg to 10 μg. The D-form of N-methyl aspartic acid was the most potent of the compounds tested. With both erythro and threo-DL-B-oxyglutamic acid as with N-methyl aspartic acid, mice developed running convulsions and the minimum lethal dose of these compounds were all about 10 μg. In general, studies suggested that N-methyl aspartic acid may be involved in excitatory neurochemical transmission and that the presence and position of the CH_3-group may be important for excitation and depression of brain function. (4 Refs.)

Department of Pharmacology
Faculty of Pharmacy
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Fuse, Osaka, Jajan

318 Axelrod, Julius. A catecholamine oxidase in the salivary gland. Federation Proceedings, 1963, 22, 388. (Abstract)

An enzyme has been found that can oxidize epinephrine to adrenochrome. The enzyme is highly localized in the salivary gland of the cat and other mammals. It is present in small amounts in skin and lung and other glandular tissues and absent in the liver and heart. The enzyme can be measured by incubating salivary gland, H^3-epinephrine, Mg^{++}, and pheniprazine, an MAO inhibitor. The hydrazine serves to trap the enzymatically formed adrenochrome to form a stable radioactive hydrazone which can be extracted into toluene

and measured. MAO inhibitors without a free hydrazine group cannot serve as a trapping agent. The enzyme has been partially purified and its properties studied. In addition to epinephrine, it also oxidizes other catecholamines. Ascorbic acid and glutathione inhibit the enzyme at low concentrations while chlorpromazine and monophenolamines stimulate the formation of adrenochrome.

National Institutes Of Mental Health
Bethesda, Maryland

319 Bessman, S. P. & Fishbein, W. N. Gamma-hydroxybutyrate -- a new metabolite in brain. Federation Proceedings, 1963, 22, 334. (Abstract)

Brain extracts have been shown to catalyze the oxidation of DPNH by succinic semialdehyde (SSA) the transamination product of GABA. The product would be gamma-hydroxybutyrate (GHB). Rat brain extracts were alkalinized to pH 11 to decompose esters and lactones. Reacidification caused lactonization of GHB which was extracted as the ether soluble lactone. Paper chromatography of the hydroxamic acid of this lactone showed it to be identical with the hydroxamic acid of gamma-butyrolactone. The concentration of the precursor and/or this lactone in rat brain is about $1\text{-}2 \times 10^{-3}$M. The enzyme which reduces SSA in the presence of DPNH is found only in the 100,000 gravities supernatant and appears identical with lactic dehydrogenase (LDH). All four hybrids or "isozymes" of LDH have the same relative activity to both pyruvate and SSA, and no SSA reacting bonds other than those corresponding to LDH are found on starch gel electrophoresis. Crystalline muscle LDH as well as brain LDH showed the same relative activity and response to inhibitors such as lactate, gamma-hydroxybutyrate, gamma-hydroxy valerate, and oxamate. There is no dissociation of activity with heat denaturation of DEAE column chromatography.

University of Maryland Medical School
Baltimore, Maryland

320 Buhler, Donald R. Metabolism of 3-(p-chlorophenoxy)-1, 2-propanediol monocarbamate (chlorophenesin carbamate), a new muscle relaxant. Federation Proceedings, 1963, 22, 540. (Abstract)

The metabolism and excretion of chlorophenesin carbamate-H^3 were studied following oral administration to rats (100 mg/kg). Within 72 hours, 80-85 percent of the dose was excreted in the urine and only 5 percent in the feces. Hydrolysis and extraction of pooled urine samples demonstrated that 59 percent of the urine radioactivity was recovered in neutral extracts and 35 percent in acidic fractions. Paper chromatographic examination of the urine extracts indicated that the major rat urinary metabolite was the glucuronide of of chlorophenesin carbamate and that the main acidic metabolites were p-chlorophenoxylactic acid. The identities of these metabolites were confirmed following isolation from subsequent large scale rat studies by a comparison of the UV and infrared spectra, elemental analyses, melting points, and Rf values with those of the authentic compounds. After oral administration of unlabeled chlorophenesin carbamate to humans (2 or 3 g), about 85 percent of the drug was excreted in the urine within 24 hours as the glucuronide of chlorophenesin carbamate. In addition, small amounts of acidic metabolites similar to those observed in the rat also were released in the urine of the test subjects.

The Upjohn Company
Kalamazoo, Michigan

321 Campos, H. A. Effect of tyramine and cocaine on the subcellular distribution of catecholamines in the isolated cat heart. Federation Proceedings, 1963, 22, 566. (Abstract)

Homogenates were separated into 3 fractions by centrifugation: "coarse sediment (2000 gravities), "particulate" sediment, and "soluble" supernatant fraction (105,000 gravities).

A "spontaneous" decrease in concentration of catecholamines occurred when the heart (Langendorff preparation) was perfused for a period of 90 minutes with Krebs-Hensleit solution. This decrease was marked in the "soluble" but negligible in the "articulate" fraction of atria. Both fractions from the left ventricle exhibited significant decreases in concentration. Perfusion with tyramine for 30 minutes markedly depleted both fractions. Low concentrations of cocaine depleted the "soluble" fractions in the atria and both fractions in the ventricle while high concentrations prevented "spontaneous" and tyramine-induced depletion. Data compatible with a primary depleting effect of tyramine on catecholamines in the "soluble" fraction were obtained from experiments in which tyramine and cocaine were employed in combination at various concentrations.

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322 Prange, Arthur J., Jr., Lopton, Morris A., & Love, G. Neil. Diminution of imipramine mortality in hypothyroid mice. Nature, 1963, (4873), 1212-1213.

Hyperthyroid mice are significantly more sensitive and hypothyroid mice significantly less sensitive than normal mice to the lethal effects of imipramine. One hundred male Swiss-Webster mice were divided into 2 groups, one on a standard diet, the other one receiving 0.2 percent propylthiouracil (PTU) in drinking water. PTU-fed mice showed retarded gain in weight. On the 16th day, the mice were given lyophilized imipramine intraperitoneally. At 100 mg/kg, 5 of 10 normal mice and 1 of 10 PTU-fed mice died. At 130 mg/kg, 12 of 20 of either group and at 165 mg/kg, 17 of 20 normal ones, and 11 of 20 PTU-fed ones died. Apparently hypothyroidism had reduced imipramine mortality. Hypothyroidism was increased in the next study. Here at 85 mg/kg 4 of 10 normal ones and 3 of 10 PTU-fed mice died. At 130 mg/kg 13 of 20 normal ones and 12 of the PTU-fed mice died within 2 hours of injection. All had preterminal signs of hyperactivity and convulsions. Statistical analysis showed that intraperitoneal imipramine has a sloping dose-mortality curve. The curves for hyper-, hypo-, and eu-thyroid mice were parallel over the dose range tested. (2 Refs.)

School of Medicine
University of North Carolina
Chapel Hill, North Carolina

323 Delgado, Jose M. R. Intracerebral chemo-stimulation in unanesthetized monkeys. Federation Proceedings, 1963, 22, 515. (Abstract)

Micro amounts of drugs were repeatedly injected for weeks into the caudate nucleus, thalamus, hippocampus, and white matter of unanesthetized monkeys. Injection of 5 µl of 1 percent acetylcholine evoked bursts of seizure like activity with a pattern typical of each structure, which started after a few minutes, and lasted for about 30 minutes, remaining localized to the injection site. Cerebral excitability was unchanged. Assemblies of double cannulas and electrodes (chemitrodes) had been previously implanted. Seizures evoked electrically did not disturb the chemically induced activity, suggesting the activation of two different sets of mechanisms. Acetylcholine perfused intracerebrally through the white matter for 1 hour could be fully recovered, while some loss existed in perfusions close to areas of hidden cortex. Acetylcholine stimulation required a minimum amount (5 µl) applied in a minimum time (1 minute). Carbachol evoked bursts of electrical activity which lasted for several days. Atropine, epinephrine, LSD, 5-HT, histamine, and other drugs were tested.

Yale University School of Medicine
New Haven, Connecticut

324 Ebert, A. G., Yale, H. L., & Hess, S. M. The metabolism of C^{14}-fluphenazine (Prolixin) enanthate. Federation Proceedings, 1963, 22, 539. (Abstract)

Fluphenazine enanthate (FE), the heptanoic acid ester of fluphenazine (F), is a potent, long-acting tranquilizer. Radioactivity in rat brain, urine, and feces was measured after a single 30 mg/kg s.c. dose of either FE or F in oil. Twenty-four hours after dosing, brains of rats receiving either F or FE contained only F, in concentrations of 3.9 µg/g and 0.4 µg/g, respectively. This represented 69 percent of total brain radioactivity in animals given F but only 31 percent of brain radioactivity in FE-treated animals. During the 10 days following F administration, 8 percent of the radioactivity administered appeared in the urine and 36 percent in feces; FE-treated animals excreted 4 percent of the administered radioactivity in urine and 13 percent in feces. Paper chromatograms of extracts of 24-hour urine samples from animals receiving FE revealed the presence of 2 radioactive spots. They were identified as F and fluphenazine sulfoxide and were present in concentrations of 0.6 µg/ml and 6.4 µg/ml of urine, respectively. These metabolites accounted for 15-30 percent of total urinary radioactivity.

Squibb Institute for Medical Research
New Brunswick, New Jersey

325 Ehrepreis, S., Muson, H. R., Gullino, M., & Cooper, H. L. A molecular basis for the action of neurotropic agents on various tissues. Federation Proceedings, 1963, 22, 215. (Abstract)

The action of neurotropic agents has been explored on single electroplax of electric eel, squid axon, and aortic strip. The parameter examined is the ability of these agents to block responses to depolarizing stimuli: electrical stimulation for electroplax and axon, K^+ for aorta. In many instances, the concentrations of drug required to block responses were very close, suggesting that they react at similar or even common binding sites. Very potent drugs, e.g., dibucaine, chlorpromazine, benadryl, etc., combine strongly with and precipitate the drug-binding protein isolated from electric organ of electric eel (Ehrepreis 1960). Similar reactions occur with extractable components of aorta and other tissues (sciatic nerve, heart, intestine, striated muscle). Other components of electroplax as well as most purified well-characterized macromolecules fail to react in a specific way with these and other drugs. It is proposed, therefore, that many agents which block depolarization of nerve, smooth muscle, etc. may produce their effects by combining with membrane components with properties similar to those of the drug-binding protein of electric tissue. It may thus be possible to isolate these drug receptors in solution.

Georgetown University Medical School
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326 Musacchio, J., Dudowitz, A., Gerber, H., & Goldstein, M. N-acetylation and demethylation of mescaline in rats. Federation Proceedings, 1963, 22, 481. (Abstract)

N-acetylation and O-demethylation represent a metabolic pathway for mescaline. A group of rats was treated with mescaline-C^{14} and the urine was collected for 24 hours. After acid hydrolysis, the urine was extracted with ethyl acetate and aliquots of the organic phase were submitted to paper chromatography in benzene-acetic acid water, (2:1:1). Radioactive peaks were found which coincided with the synthetic N-acetyl-3, 5-dimethoxy-4-hydroxyphenylethylamine (I), N-acetyl-3, 4-dimethoxy-5-hydroxphenylethylamine (II) and

Nacetylmescaline (III). One other radioactive peak was not completely identified, but the chromatographic behavior suggests that it is N-acetyl-3, 4-dihydroxy-5-methoxy mescaline (IV). Treatment with iproniazid increased the excretion of I, II, III, and IV, and decreased the excretion of the acidic metabolites. Compounds I and II were further identified by their color reactions with phenolic reagents and by their chromatographic behavior as free amines obtained after alkaline hydrolysis and as N,O-acetylated derivatives. When rats were treated with III, the only metabolites isolated were I, II, and IV. This suggests that N-acetylation precedes O-demethylation.

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327 Ober, R. E., Gwynn, G. W., Chang, T., McCarthy, D. A., & Glasko, A. J. Metabolism of 1-(1-phenylcyclohexyl) piperdine (Sernyl). Federation Proceedings, 1963, 22, 534. (Abstract)

Phencyclidine (Sernyl) labeled with C^{14} or H^3 was used in rhesus monkeys. After single i.v. doses of 2-6 mg/kg, about 60 percent of the C^{14} appeared in the urine in 12 hours and about 75 percent in 8 days. Fecal recovery was 1-2 percent and no $C^{14}O_2$ was found in expired air. Chromatographic analysis of both urine and plasma revealed some unchanged phencyclidine and much larger amounts of metabolites. The major metabolite, present in urine as a conjugate, was isolated and identified as a nonphenolic, dihydroxy phencyclidine. Phenylcyclohexene and a conjugated monohydroxy phencyclidine were chromatographically identified as minor urinary metabolites. The dihydroxy had no detectable phencyclidine-like pharmacologic activity in either the free or conjugated form. No metabolites were detected in central or peripheral nerve tissue and about equal concentrations of phencyclidine were found in sciatic nerve, spinal cord, and various brain areas. Gas chromatography of urine extracts from species other than monkey revealed differences in the relative amounts of unchanged phencyclidine and its mono and dihydroxy metabolites.

Research Laboratory
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Ann Arbor, Michigan

328 Pineda, Anselmo, & Snider, Roy S. Nonspecific depressant action of serotonin on brain stem and cerebellum. Neurology, 1963, 13, 166-176.

The depressant effect of 5-HT (serotonin) on evoked potentials in the cerebullum and cerebrum following peripheral nerve stimulation was studied in 22 cats, weight 1.8 to 3.66 kg. Doses of 10 µg 5-HT and d, l-5-HTP were used, and the routes of administration were cerebellomedullary cistern, lateral ventricle, and contralateral or ipsilateral carotid arteries in the neck. To induce change, doses up to 50 mg of d, l-5-HTP were given i.v. in the hind legs. The depressant effect was also found present in the following thalamic nuclei: ventroposterolateralis, ventrolateralis, medialis dorsalis, centralis lateralis, and centrum medianum. There was, however, prolonged delay of action or no effect in the mesencephalic reticular formation with 10 µg/kg. When higher doses were used (20 to 40µg/kg), the animals suffered from respiratory arrest and death. When artificial respiration is used, there is first a diminution of amplitude, then a total reappearance of the evoked response. The evoked responses return to normal before the respiratory system is active enough to maintain respiration. This information is interpreted to indicate that serotonin has a general nonspecific effect on the CNS.

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329 Pletscher. A. & Gey, K. F. The effect of a new decarboxylase inhibitor on endogenous and exogenous monoamines. Biochemical Pharmacology, 1963, 12, 223-228.

Investigations on the mode of action of Ro 4-4602 in vivo on endogenous and exogenous monoamines in various animal species are reported. In mice, rats, and guinea pigs, the hydrazine Ro 4-4602, a potent irreversible inhibitor of decarboxylase of aromatic amino acids, decreased 5-hydroxytryptamine and norepinephrine in the brain, and decreased norepinephrine in the heart by a maximum of about 50 percent as measured spectrophotoflurometrically. In rats, the 5-hydroxytryptamine increase in brain and heart induced by 5-hydroxytryptophan as well as recovery of 5-hydroxytryptamine in the brain after its depletion by Ro 4-1284 is completely inhibited by the drug. The possibility is discussed that Ro 4-4602 might interfere mainly with the metabolism of "free" and relatively little with that of "stored" amines. "Free" is used as equivalent to "more easily available for the metabolizing enzymes as compared with the stored amines."

Med Res. Dept. of F. Hoffmann-La Roche & Co. Ltd.
Basle, Switzerland

330 Posner, Herbert S., Culpan, Roger, & Levine, Jerome. The phenolic metabolites of promazine and chlorpromazine in human urine. Federation Proceedings, 1963, 22, 540. (Abstract)

When expressed as percent of administered dose of chlorpromazine, humans excrete 2-3 times as much of phenolic than of non-phenolic metabolites. The phenols are found almost completely in conjugation with glucuronic acid. There are at least 5 phenolic metabolites of chlorpromazine; monophenolic derivatives of chlorpromazine and its mono- and di-N-demethylated derivatives and monophenolic derivative which appears to be neutral. A dioxygenated metabolite is also present. In the case of promazine, where the 4 isomeric hydroxy derivatives are now available, it has been shown by color reaction with 2, 6-dichloroquinone chloroimide, that monohydroxylation occurs at the 3- position rather than at the 1-, 2-, or 4-positions. Chlorpromazine, however, is not hydroxylated in an analogous manner. Spectrographic analysis of the color of reference phenothiazines with 50 percent H_2SO_4 (v/v), based on the principles of additive and constitutive properties of molecules, and color with 2,6-dichloroquinone chloroimide, suggest that the monophenolic metabolites of chlorpromazine possess the 2-chloro-8-hydroxy structure. On the basis of the sulfuric acid reaction, it is suggested that the dioxygenated metabolite possesses the 2-chloro-7,8-dioxygenated structure.

Clinical Neuropharmacology Research Center
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331 Roizin, L. Mitochondria (pleomorpho metalbolosomes) as histometabolic gradients. (Effects of prochlorperazine on the rat brain as revealed by electron microscope). Diseases of the Nervous System, 1963, 24, 61-66.

Electron microscope studies of the cerebral cortex of rats injected with prochlorperazine showed outstanding ultracellular alterations of submitochondrial components and the whole mitochondrion. The concept of patterns of neuropathogenic mechanisms from cell to molecule is postulated as a working hypothesis. The cerebral mitochondria of 3 groups of male albino rats were examined between 2 and 18 hours after injection with 2.5 mg/100 gm.b.w. and 5 mg/100 gm.b.w. prochlorperazine (Compazine, S.K.F.). Structural changes of the mitochondrial membrane, the mitochondrial matrix and cristae mitochondrialis seem to be related to the pharmacodynamic effects of prochlorperazine. It is suggested that the changes are associated with

alterations of the respective molecular arrangement of which they are composed and, therefore, may be used as structural and histometabolic gradients. The mitochondria (pleomorpho metabolosomes) seems to be a very sensitive biological tool, which may be used in the study of neurophysiologic and neuropathogenic mechanisms of ultracellular and molecular levels. (49 Refs.)

Department of Pathology
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New York, New York

332 Rosell, A. & Axelrod, J. Release and metabolism of H^3-norepinephrine (NE) in skeletal muscle. Federation Proceedings, 1963, 22, 508. (Abstract)

Infused levarterenol (norepinephrine) is retained in the isolated dog gracilis muscle and then released at a slow rate. Of the total radioactivity (H^3) in the effluent, only 23 percent was levarterenol, 22 percent was normetanephrine, and 45 percent was VMA plus the O-methylated glycol. Little or no deaminated catechols were found. Sympathetic nerve stimulation (Stim) at 3-12/second resulted in delayed elevation of H^3, almost all of which was levarterenol. Delayed outflow of H^3 and levarterenol is presumably due to a decrease in transcapillary transport (PS) (1962). Released levarterenol appears to be trapped in the tissue and a portion may return to the store. Stim after dibenzyline resulted in an immediate and larger elevation of H^3 and levarterenol. No net change in metabolites was observed. After dibenzyline, PS is unaltered and released levarterenol immediately appears in the effluent. The absence of an increase in metabolites of levarterenol after Stim indicates that enzymatic inactivation in skeletal muscle plays a minor role in the termination of the effects of levarterenol. Inactivation of levarterenol appears to be due to entry into the store or the circulation.

National Institute of Mental Health
Bethesda, Maryland

333 Rosenberg, Franklin J. & Savaris, Peter J. Reversal of chlorpromazine depression. Federation Proceedings, 1963, 22, 568. (Abstract)

One hour after 12.5 mg/kg i.p. of chlorpromazine mice are prostrate and cannot remain for 10 seconds with their forepaws on a horizontal bar raised 1 3/4 inches off the surface. Fifteen minutes after i.v. histamine, the mice not only remain at the bar but balance and walk on it (ED_{50}=47 mg/kg, minimum lethal dose = 200 mg/kg). Rather than blocking the histamine effect, antihistamines synergized with histamine and themselves reversed chlorpromazine depression at i.p. doses 1/4 to 1/10 minimum lethal doses (Doxylamine, Chlorphenamine, Rhenindamine, Thenyldiamine, Tripelennamine). Diphenhydramine was inactive. Trihexyphenidyl, imipramine, amitriptyline were inactive. Dexamphetamine was effective. According to Paton, amphetamine and antihistamines are histamine liberators. If antihistamines do not block the CNS effects of histamine but do release it, the paradox of histamine-antihistamine synergism can be explained.

Sterling-Winthrop Research Institute
Rensselaer, New York

334 Glende, Eric A. & Cornatzer, W. E. The effect of chlorpromazine, trifluoperazine and promethazine on brain sulfalipids. Journal of Pharmacology and Experimental Therapeutics, 1963, 139, 377-382.

Biochemical effects of chlorpromazine, trifluoperazine, and promethazine on the incorporation of S35 (sodium sulfate) and (C14)-l-galactose into brain sulfalipids are related to their chemical structure rather than their pharmacological actions. A check had been made on the effect of the three phenothiazine derivatives in vivo, on

the labeling of rat brain sulfalipids with (S35) and the effect of chlorpromazine and trifluoperazine on the incorporation of (C14)-1-galactose into cerebrosides. The whole brain of male rats was used for the study. Chlorpromazine at 5 mg and 20 mg/kg, trifluoperazine and promethazine both at 20 mg/kg inhibited the uptake of S35. Chlorpromazine at 3 mg/kg and trifluoperazine at 5 mg and 3 mg/kg had no significant effect on S35 incorporation into brain sulfalipids. Promethazine, an antihistaminic compound, was chosen as a comparison with the two tranquilizers, because its pharmacological actions differ from the other two phenothiazine derivatives. Its effect on S35 labeling of brain lipids was quite similar. The results indicate, therefore, that the decrease of S35 labeling combined with an inhibition of oxidative phosphorylation by the three phenothiazine derivatives is related to their basic chemical structure and not their pharmacological action. Chlorpromazine and trifluoperazine both at 20 mg/kg decreased the incorporation of (C-14)-1-galactose into the total lipid fraction, galactose, and fatty acid fractions of a purified lipid extract. (25 Refs.)

Department of Biochemistry
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335 Schallek, William & Kuehn, Alfred. Effects of trimethadione, diphenylhydantoin, and chlordiazepoxide on after-discharges in brain of cat. Proceedings of the Society of Experimental Biology and Medicine, 1963, 112, 812-817.

Chlordiazepoxide, trimethadione, and diphenylhydantoin, clinically effective agents in neurological disturbances, are found to significantly affect certain portions of the brain, specially the thalamic nuclei, hippocampus, and cortex. Forty-one cats were prepared under anesthesia in order to test the effects of trimethadione, diphenylhydantoin, and chlordiazepoxide (Librium) on certain portions of the brain. Trimethadione 100 mg/kg i.v. was found to raise the threshold of the central lateral nucleus. of the thalamus of the cat. The drug had no effect on medial dorsal nucleus, cortex, or hippocampus. Diphenylhydantoin 10 mg/kg decreased duration of response in cortex and hippocampus but not in the thalamus. Chlordiazepoxide 10 mg/kg raised threshold and decreased duration and amplitude of response in the central lateral nucleus. Diphenylhydantoin differs clinically from trimethadione in being effective in grand mal rather than in petit mal epilepsy; in the laboratory it differs in lacking any threshold-raising ability in animals, when minimal seizures or EEG signs of seizures are taken as the end point.

Department of Pharmacology
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336 Sloan, Jewell W., Brooks, J. W., Eisenman, Anna J., & Martin, W. R. The effect of addiction to and abstinence from morphine on rat tissue catecholamine and serotonin levels. Psychopharmacologia, 1963, 4, 261-270.

Chronic intoxication of the rat with large doses of morphine significantly alters metabolism of brain catecholamines by adaptively increasing their rate of synthesis. On withdrawal of morphine, there is either an increase in utilization of brain catecholamines or an abrupt slowing of the synthesis rate or both. Four groups of Wistar albino rats, 36 animals in each group, were experimentally addicted to morphine sulfate on a rapidly increasing dosage schedule which ranged from 5 mg/kg/day to 160, 260, and 400 mg/kg/day, respectively. Twelve control animals in each group received saline injections. While addicted animals showed a failure to gain body-weight, their brain weights did not change nor did their heart-weight decrease significantly. Spleens weighed less in test animals than controls and the adrenal glands were hypertrophied. Heart and splenic

catecholamines decreased, but splenic serotonin was significantly elevated during addiction. (16 Refs.)

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337 Smith, A. A. & Wortis, S. Bernard. Effect of tolbutamide on norepinephrine catabolism. Federation Proceedings, 1963, 22, 390. (Abstract)

In the guinea pig treated with 200 mg tolbutamide/kg, dl-norepinephrine-7-H3 is converted almost quantitatively to m-hydroxyphenylacetic acid (MHPAA). Iproniazid inhibits this reaction. After injection of labeled normetanephrine both vanillylmandelic (VMA) and MHPAA appear in the urines of treated guinea pigs. Larger doses of normetanephrine yield VMA, MHPAA, and homovanillic acid (HVA). The glycol catabolite of levarterenol which possesses adjacent aliphatic hydroxyls is also converted to MHPAA but iproniazid does not inhibit this reaction. In preliminary experiments, epinephrine was found to catabolize conventionally although dopamine yielded MHPAA but no HVA. The above findings suggest that beta-dehydroxylation requires an adjacent hydroxyl or primary amine; conversion of substantial proportions of normetanephrine to MHPAA further suggests the occurrence of extensive O-demethylation.

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338 Smith, C. B. Effect of d-amphetamine upon the amine content of the mouse brain. Federation Proceedings, 1963, 22, 568. (Abstract)

The correlation between changes in locomotor activity and changes in the brain content of levarterenol, dopamine (DA), and 5-HT produced by dexamphetamine were studied in mice. Doses of dexamphetamine ranging from 3-30 mg/kg increased locomotor activity. Maximal activity was attained with the 10 mg/kg dose; this dose did not produce convulsions and was about 30 percent of the LD_{50}. This amount caused a 20.2 percent decrease in brain levarterenol, no significant change in brain DA, and a 21.6 percent rise in 5-HT. These changes were compared with changes in brain levarterenol, DA, and 5-HT produced by pipradrol and cocaine. The increase in locomotor activity produced by cocaine and pipradrol were as large or larger than those produced by dexamphetamine. However, no changes in brain levarterenol, DA, or 5-HT were observed at doses which caused maximal increases in locomotor activity. The studies show that increases in locomotor activity produced by dexamphetamine are accompanied by a decrease in brain levarterenol and an increase in brain 5-HT, but suggest that increased activity as such does not result in the changes in brain amines.

Department of Pharmacology
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339 Smith, Emil R. The effect of norepinephrine infusions upon some responses of reserpine-treated spinal cats to tyramine. Journal of Pharmacology and Experimental Therapeutics, 1963, 139, 321-329.

Action of tyramine may be enhanced where there is increased extracellular norepinephrine but may not be explained solely by an ability to release norepinephrine from tissue stores. Responses were recorded of untreated and reserpine-treated spinal cats to tyramine administered after norepinephrine infusions but before recovery, and after recovery from norepinephrine infusions. Responses of the nictitating membrane, blood pressure, and heart rate to tyramine were reduced by pretreatment with reserpine, but responses of the

nictitating membrane to norepinephrine were unchanged and the cardiovascular responses were enhanced or unaltered. Tyramine given after recovery of untreated cats infused with norepinephrine were not different from tyramine given before such infusions. Norepinephrine infusions of reserpine-treated cats enhanced but did not restore the nictitating membrane and blood pressure while the chronotropic responses were restored. After termination of norepinephrine infusions but before recovery, administration of tyramine enhanced the nictitating membrane and blood pressure of reserpine-treated cats.

Mason Research Institute
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340 Sprince, Herbert, Dawson, John T. Jr., & Gorin, Nathaniel H. Inhibition of cholinesterase by indolepyruvic acid. Federation Proceedings, 1963, 22, 335. (Abstract)

The indolealkylamines, tryptamine and 5-HT are known to inhibit cholinesterase activity. The experiment was run to determine if alpha-keto acids (indolepyruvic acid or 5-hydroxindolepyruvic acid) have similar action. The anticholinesterase activity of indolepyruvic acid was measured and compared with that of its corresponding amine (tryptamine) and certain other alpha-keto acids implicated in neurological diseases of childhood (e.g., phenylpyruvic acid or alpha-keto isocaproic acid). An adaptation of Hestrin's method was used. Indolepyruvic acid inhibited the activity of purified serum pseudocholinesterase (Cutter) by 50 percent at 10^{-4}M concentration; tryptamine, by 50 percent at 10^{-3} M; phenylpyruvic acid, by 36 percent at 10^{-3} M; alpha-ketoisocaproic acid by 17 percent at 10^{-3} M. Indolelactic acid and indolepropionic acid showed negligible inhibition at 10^{-3} M. Therefore, the effective concentration of indolepyruvic acid appears to be specific. The increased activity of indolepyruvic acid is interpreted as due to its ability to attach itself to both the anionic and esteractic sites of the pseudocholinesterase molecule, whereas the other inhibitory compounds can attach to only one of either of these sites. Inhibitory action was considerably less with purified "true cholinesterase" from bovine red blood cells.

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Coatesville, Pennsylvania

341 Levine, Robert J. & Sjoerdsma, Albert. Direct measurement of monoamine oxidase inhibition in humans. Clinical Pharmacology and Therapeutics, 1963, 4, 22-27.

Oral administration of isocarboxazid and oral and i.v. administration of pargyline (MO-911) produced marked MAO inhibition in human jejunal mucosa. Correlative studies with MO-917 in rats suggested that MAO inhibition is also present in other tissues. Man seems to be more sensitive to MAO inhibitive drugs than several other mammalian species. Nine adults with diagnoses of hypertension (5), arteriosclerotic heart disease (3), hypothyroidism were submitted to oral biopsy to obtain jejunal mucosa for the purpose of an assay of MAO activity before, during, and after administration of two MAO inhibitive drugs. Tissue MAO-levels were correlated with urinary levels of tryptamine, one of the substrates of the enzyme. Oral and parenteral routes of drug administration were compared. The 2 drugs were isocarboxazid (hydrazine-type) and MO-911 (pargyline hydrochloride). MAO activity was also studied in the heart, liver, brain, stomach, and jejunum of the rat. Most of the MAO activity in humans is in the liver and gastrointestinal mucosa. In rats, these tissues are least sensitive. The average MAO inhibition by MO-911 in man was 92 percent by isocarboxazid 83 percent. Oral administration and intravenous administration

of MO-911 were similar, though MAO inhibition was slightly greater in i.v. administration with smaller doses. In rats, a higher dose level such as 100 mg/kg compared to an initial 12.5 mg/kg, 90 percent inhibition was found in all rat tissue examined. The direct assay method of tissue MAO is recommended. In the human studies, MAO inhibiting drugs have been shown to produce orthostatic hypotension, the mechanism of which is still unknown. (9 Refs.)

National Heart Institute
National Institutes of Health
Bethesda, Maryland

342 Vanov, S. Effect of monoamine oxidase inhibitors on the pressor response to normetanephrine in the rat. Archives Internationales de Pharmacodynamie et de Therapie, 1963, 141, 62-66.

Monoamine oxidase (MAO) inhibitors failed to potentiate or prolong the pressor effect of normetanephrine in rats. In this study, experiments on the blood pressure of 28 anesthesized adult albino rats were carried out. The animals were injected with heparine (500 IU/100 gm b wt). Drugs were administered via the jugular vein. At the start of each experiment, normetanephrine (3-O-methylnoradrenaline) was injected. A marked pressor effect was achieves by doses of 0.1-1 mg per rat. The MAO inhibitors, which were then administered, consisted of iproniazid phosphate (50-100 mg/kg), nialamide (40 mg/kg), phenelzine dihydrogen sulphate (10 mg/kg), and tranylcypromine hydrochloride (10 mg/kg). These injections were followed by a reinjection of normetanephrine at intervals of 30-90 minutes. Normetanephrine exerts a short-lived pressor effect, because it is an inactivation product of noradrenaline. Its action on rat blood pressure is about one-thousandth of that of noradrenaline. Since the MAO inhibitors did not potentiate the pressor effect, the author suggests that the inactivation of large doses of normetanephrine is probably not the subject of enzymatic degradation through MAO, but of some other factors. (4 Refs.)

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343 Van Rossum, J. M. Mechanism of the central stimulant action of alpha-methyl-meta-tyrosine. Psychopharmacologia, 1963, 4, 271-280.

Studies in mice showed that (1) the psychomotor stimulant action of α-methylmetatyrosine is produced after some delay by its metabolic amines, (2) the two analogous amino acids α-methyl DOPA and α-methyltyrosine do not exert psychomotor stimulant action but inhibit the effect of DL-α-methylmetatyrosine (α-MMT). Two male albino mice were studied for spontaneous locomotor activity by a modified Dews' light beam method. Drugs were injected intraperitoneally in doses of 200 - 1000 μ mol/kg. D-amphetamine was used as a reference drug in a dose of 5.62 μ mol/kg. The results of the study reveal that α-MMT acts by virtue of metabolites, mostly (+)3-hydroxy-amphetamine or metaraminol, formed in the brain while these metabolites act by releasing catecholamines from storage sites. The author also concludes that α-MMT acts through metabolites, mostly (+)3-methoxyamphetamine, formed in the liver, while these metabolites act directly on receptors for catecholamines in the brain. (20 Refs.)

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344 Waddell, W. J. The metabolic conversion of secobarbital to 5-(1-methylbutyl) barbituric acid and to 5-(2, 3-dihydroxypropyl)-5-(1-methylbutyl) barbituric acid. Federation Proceedings, 1963, 22, 480.

The deallylated metabolite was isolated

from the urine of dogs given secobarbital i.v. in large doses. Paper chromatograms of extracts of urine from patients who had taken secobarbital revealed a barbituric acid derivative with an R_f value identical to that of the deallylated metabolite. The UV spectra were typical of a barbituric acid with 1 substitution in the 5-position. The infra-red spectrum was identical to that of synthetic 5-(1-methylbutyl) barbituric acid. The melting point of 162.8-164.4° was not lowered by admixture with the synthetic. Elemental analysis: 54.6 percent C, 7.0 percent H, 16.4 percent N (calculated 54.5 percent C, 7.1 percent H, 14.1 percent N). The glycol was isolated from the urine of a man who had ingested secobarbital. UV spectra were typical of a barbituric acid disubstituted in the 5-position. The compound gave negative permanganate and iodoform tests and had neither a carboxyl nor a carbonyl group. It gave a positive periodic acid test and the IR spectrum was identical to that of synthetic material prepared by permanganate oxidation of secobarbital. The melting point of 156-157° C was not lowered by admixture with the synthetic. Elemental analysis: 52.7 percent C, 7.2 percent H (calculated 52.9 percent C, 7.4 percent H).

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345 Wallenius, Gunnar, Zaar, Bertie, & Lausing, Endel. A rapid method for determination of barbiturate in serum of urine. The Scandinavian Journal of Clinical and Laboratory Investigation, 1963, 15, 252-256.

A very simple yet accurate method for determining barbiturate levels in serum and/or urine has been made available through the investigations of the authors, at the University Hospital, Uppsala, Sweden. Described is a rapid and simple method for determination of barbituric acid derivatives in serum and urine, using a new extraction principle, which when utilized in combination with the ability of barbituric acid to form a complex with mercuricions, produces a quantitated complex with a reagent called dithizone. The only drugs known so far to interfere with the method are 4-ethyl-4-methyl-2.6-dioxopiperidine (Malysol), 3-phenyl-3-ethyl-2.6-dioxipiperidine (Doriden), and some hydantoin derivatives. An analysis requires approximately 5 minutes and gives sufficiently accurate results for the detection of barbiturate poisoning.

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University Hospital
Uppsala, Sweden

346 Weil-Malherbe, H., Smith, E. R. B., Eisenman, A. J., & Fraser, H. F. Urinary excretion of catecholamines and some of their metabolites during a course of morphine addiction and withdrawal in two human subjects. Federation Proceedings, 1963, 22, 567. (Abstract)

The excretion of catecholamines (epinephrine, levarterenol and dopamine) and of some metabolites (metanephrine, normetanephrine, 3-methoxy -4-hydroxymandelic, 3,4 dihydroxymandelic and 3,4-dihydroxyphenylacetic acids) was determined in 2 volunteers who, after a preliminary observation period of 30 days, received increasing doses of morphine s.c., reaching a maximum of 250 mg/day after 17 days. This level was maintained for a further 81 days in subject 1 and 20 days in subject 2. Observations were continued during a withdrawal period (7 days) and recovery period (case 1: 22 days, case 2: 60 days). The excretion of most metabolites was increased during the incremental, as well as the plateau phase of addiction, in both subjects. In subject 1 levarterenol excretion, and in subject 2 epinephrine excretion, was increased during the incremental phase; dopamine excretion was increased in both subjects. Contrary to expectation, the excretion data did not indicate any significant sympatho-adrenal

activation during the withdrawal phase.

Saint Elizabeths Hospital
Washington, D.C.

347 Weiner, Norman. Synthesis of dinitrophenyl (DNP)-catecholamines and DNP-dihydroxyphenylalanine (DOPA). Federation Proceedings, 1963, 22, 390. (Abstract)

At 70° C, in the presence of ethanolic fluorodinitrobenzene (FDNB), $NaHCO_3$, and $NaHSO_3$, DNP derivatives of DOPA, dopamine, levarterenol and epinephrine have been synthesized and the products extracted into ethyl acetate. After removal of solvents by vacuum distillation, the solids are redissolved in ethyl acetate and dinitrophenol is removed by extraction into dilute Na_2CO_3 solution. The DNP-amines are precipitated by addition of cyclohexane and purified by recrystallization. The products behave like single compounds when chromatographed, either on silica gel columns or by means of thin-layer chromatography.

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348 Weltman, A. S., Sacker, A. M., Steinglass, P., & Bernstein, M. Endocrine effects of lysergic acid diethylamide on male rats. Federation Proceedings, 1963, 22, 165. (Abstract)

LSD-25 responses of male Wistar rats were assayed; test animals were given 8 s.c. injections of LSD-25 (500 or 750/kg) on alternate days for 2 weeks, except for the last dose. Prior to autopsy, urinary, steroid, tail blood, body weight, food, and oxygen consumption levels were studied. Depending on time and dosage, LSD-25 induced significant increases in 17-ketosteriod levels and moderate increases in 17-hydroxycorticosteroid values. Marked or significant decreases were noted in white blood counts and eosinophilia, body weight gains, food and oxygen consumption. Analyses revealed significantly lower absolute splenic, liver and thyroid weights with consistent smaller reductions in the seminal vesicle and thymic weights. Adrenal weights were significantly heavier with the lower dose. The organ weight, steroid, white blood count, food, and oxygen consumption data corroborate that LSD-25 stimulates adrenal activity and inhibits metabolic, gonadal, and thyroidal function. Sex and dose response differences, as well as similarities of LSD-25 intoxication to schizophrenia, are noted.

Laboratory for Therapeutic Research
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349 Williams, R. T. Detoxication mechanisms in man. Clinical Pharmacology and Therapeutics, 1963, 4, 234-254.

Rates of biochemical reactions may differ between man and animals, indicating that drug testing may have to be done on a larger variety of species to spot toxic effects in man. Reactions of foreign compounds found in animals also occur in man, but there can be differences in rates of reactions which may have profound effects on drug action. These reactions consist of various oxidations, reductions, hydrolyses, and conjugations carried out by enzymes, many of which are located in the liver. Various groups of people may also vary from one another in their ability to metabolize drugs. Variation in drug metabolism could be due to age, sex, genetic makeup, effect of one drug upon another, or prolonged administration of one drug.

Department of Biochemistry
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350 Woolley, D. W., & Gommi, B. W. Deficiency of serotonin receptors in galactose poisoning and its possible relationship to idiocy. Federation Proceedings, 1963, 22, 624. (Abstract)

To test the idea that a lack of receptors for 5-HT (serotonin) in infancy may be the cause of mental failure in galactosemia, just as 5-HT deficiency in adult life can lead to depression and other psychiatric disturbances, the 5-HT receptors were measured quantitatively in rats suffering from galactose poisoning. The 5-HT receptor is known to be a complex lipid. It was postulated that the normal biosynthesis of this lipid (probably a galactolipid) may have been inhibited by excessive galactose or Gal-1-P. Weanling rats were fed stock diet which contained 33 percent galactose. After 2 months the stomachs were removed, and 5-HT sensitivity measured quantitatively. Control rats receiving glucose instead of galactose were tested similarly. The stomachs of galactose-treated rats were on the average 50 times less sensitive to 5-HT. Sensitivity to acetylcholine was also measured but found not to differ in the two groups. This showed that the receptor deficiency was specific for 5-HT. By contrast to these findings with stomachs, the uteri of the galactose rats did not differ from normal in sensitivity to 5-HT or acetylcholine.

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New York, New York

351 Zsigmond, Elmer K., Foldes, Vera M., & Foldes, Francis F. The in vitro inhibitory effect of psilocybin and related compounds on human cholinesterases. Psychopharmacologia, 1963, 4, 232-234.

Comparison of the anticholinesterase activity of psilocybin, bufotenin, and 5-hydroxytryptamine in human plasma, red cells, and grey matter homogenate indicates that there is no correlation between the in vitro anticholinesterase acitivity and the hallucinogenic effect of the compounds. The inhibitory effect of the compounds on the hydrolysis of acetylcholine (ACh) and butyrylcholine (BuCh) by plasma cholinesterase (PChE), on that of ACh and acetyl-β-methylcholine (MeCh) by red cell cholinesterase (RChE), and on that of ACh, MeCh and BuCh by human gray matter homogenate, was investigated. A manometric method described in a previous publication was used. The two hallucinogenic compounds had a greater inhibitory effect on the hydrolysis of acetylcholine and butyrylcholine by plasma cholinesterase and on that of butyrylcholine by the butyrylcholinesterase of gray matter homogenate than serotonin. The inhibitory effect of psilocybin and bufotenin on the hydrolipis of ACh and MeCh by RChE and by the acetylcholinesterase of gray matter homogenate was the same as that of serotonin. (10 Refs.)

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352 Weiss, Benjamin. Metabolism of DOPA-C-14 in the normal and alpha-methyldopa treated mouse. Federation Proceedings, 1963, 22, 540. (Abstract)

At various time intervals after i.p. injection of DL-3,4-dihydroxyphenylalanine-2-C^{14} in mice, the catechol metabolites were extracted from the entire animal, separated by the solvent-reversal technique of paper chromatography, and quantitated. DOPA had a biological half-life of approximately 15 minutes. One hour after the injection of DOPA-C^{14} the following labeled catechols were found (concentrations expressed as percent of total recovered radioactivity): DOPA (15 percent), dopamine (13 percent), dopac (1 percent), levarterenol (1.5 percent), epinephrine (<1percent). Residual activity was considered to represent non-catechols. Intraperitoneal injection of 6 mg/kg of α-methyldopa significantly inhibited, the decarboxylation of DOPA as evidenced by the decreased formation of dopamine. Larger doses, up to 200 mg/kg resulted in progressively greater inhibition. Time-response studies performed with 200 mg/kg of α-methyldopa indicated maximal activity in this in vivo system between 15-30 minutes; inhibitory activity persisted for about 8 hours.

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353 Pevaroff, Sherwin B., Hamelberg, William, & Bosomworth, Peter P. Circulatory effects of intravenous trimethobenzamide, hydrochloride, perphenazine, and prochlorperazine. Journal of Oral Surgery Anaesthesia, and Hospital Dental Service, 1963, 21, 24-29.

Results of a study conducted on several dogs and five humans indicate that there are minimal hemodynamic effects from trimethobenzamide, hydrochloride, perphenazine, and prochlorperazine when administered intravenously in the usual antiemetic dose. The hemodynamic effects of trimethobenzamide, perphenazine and prochlorperazine were studied in animals and humans. The study in normothermic dogs showed no significant changes in arterial pressure, EKG, contractile force of the heart or venous pressures. Trimethobenzamide (Tigan) showed less myocardial contractile force depression than perphenazine (Trilafon), and prochlorperazine (Compazine) in hypothermic dogs. Experiments in pentobarbital anesthestized dogs suggest that antiemetics should be administered cautiously to patients who are hypothermic. The observations in normothermic humans did not demonstrate any significant cardiovascular changes. The antiemetics were tolerated well when administered intravenously to anesthetized patients. In unanesthetized humans, prochlorperazine occasionally resulted in drowsiness. The intravenous dosage of the antiemetics selected in this study was calculated to be approximately one-half the recommended intramuscular dose.

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PSYCHOPHARMACOLOGY ABSTRACTS

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PSYCHOPHARMACOLOGY ABSTRACTS

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354 Hordern, Anthony,& Hamilton, Max. Drugs and "moral treatment." British Journal of Psychiatry, 1963, 109, 500-509.

The advent of the phenothiazines as a treatment modality in psychiatry has been hailed as a great advance in many quarters but is exposed to serious critical study in this review of the treatment of mentally ill patients. The use of phenothiazines as a treatment for chronic schizophrenics is only one of the various treatments available for the mental hospital chronic patient and should be employed in combination with, rather than in place of, the other treatment modalities. A review of the treatment programs of the past based on Eli Todd's concept of "moral treatment of the insane persons" described in 1826 is undertaken in this article and reveals the success obtained with such treatment modalities as group nursing, physical therapy, planned activities with graded incentives, recreational and occupational therapy, rehabilitation and aftercare programs, and intensive psychotherapy. The key to these time-tested treatment programs is that they promote interpersonal relationships between patient and staff and morale and enthusiasm are generally higher. In general, the results obtained with the phenothiazines have not improved on the results of those pioneers who introduced the "moral" treatment over a century ago. The history of medicine reveals that the enthusiasm with which a new treatment is greeted is not necessarily a measure of its efficacy. (42 Refs.)

Mental Health Research Institute
Victoria, Australia

355 Tanner, Henry, Weinberger, Julius,& Blumenthal, Irving, J. Long-term progress of hospitalized schizophrenic patients on ataractic drugs. Journal of Neuropsychiatry 1963, 4, 321-330.

A statistical study of 65 psychiatric patients who received long-range medication with ataractic drugs is presented. Though the general hospital atmosphere was improved and patients "felt better," it was concluded that the discharge rate was not significantly different from that of preshock-treatment years. Sixty-five patients, 20-45 or more years of age, were diagnosed as schizophrenic of the chronic undifferentiated, the paranoid, the catatonic, the hebephrenic, and schizo-affective types and as manic depressives of the manic type. Chronic brain syndrome, as well as emotionally unstable personality, was also represented. About 80 percent of the group had ECT or ICT, or both, prior to drug therapy. Thus the effect of these methods could be compared with the treatment with ataractic drugs. The ataractic drugs given were Thorazine, Serpasil, Equanil, Compazine, Stelazine, Trilafon, Vesprin, Tofranil, and Mellaril. Long-term treatment with these drugs yielded a more reliable picture because improvements achieved after a few months are not necessarily sustained. Where treatment relied on milieu and drug therapy, the discharge rate was not greater than that of former years. Twenty-six percent of all patients treated remained unimproved. The main success lay in quieting down patients. It is suggested that psychotherapy in groups or for individuals should be added to increase the discharge rate. Also newer therapies should be tried on a large scale such as remotivation, day or night hospitals, modern methods of hypnotic treatment, and/or hypoanalysis and vocational training. Closer rapport should be established with hospitalized patients to learn more about their individual problems.

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PS

356 Laurence, D. R. Patient selection nd stratification in therapeutic trials. linical Pharmacology and Therapeutics, 963, 4, 381-389.

his article presents a review of some tudies in which selection and stratifica- ion of patients either detracted from or dded to the ability to generalize the esults. The formal therapeutic trial is iven as the only available means to formu- ate generalizations with maximum applica- ility while the minimum of labor and atients is utilized. Clinical impression s condemned as inadequate. Examples of good nd bad practice are cited involving problems f accurate and unambiguous definition of he disease or symptom treated, the inclusion r exclusion of placebo-reactors, preexperi- ental and postexperimental investigation of ubjects who fail to complete a trial, the elation of total number to generalization nd stratification. It is suggested that herapeutic trials with groups of mental atients are particularly difficult with espect to diagnosis, generality of results ased on hospital admission criteria, and ailure to complete experimental trials. 37 Refs.)

edical Unit, University College ospital Medical School niversity College ondon, England

357 Kris, Else B. Aftercare and rehabili- ation of the mentally ill. Current Therapeu- ic Research, 1963, 5, 24-30.

day-by-day approach is suggested to ehabilitation problems of the mentally ill eleased from hospitals. Maintenance harmacotherapy with phenothiazine deriva- ives, sometimes in connection with anti- epressive drugs, is suggested in order to ridge the period of readjustment. Factors or relapse include the attitude of family nd community and difficulties in finding mployment. Better planning for these patients s necessary in regard to vocational rehabili- ation, sheltered workshop facilities, supervised residences of the boarding-house type for those without family, and family care programs. Social clubs and community centers are recommended. The latter should provide supervision of pharmacotherapy and supportive psychotherapy.

State of New York
Department of Mental Hygiene
New York, New York

358 Nodine, John H., & Slap, Joseph, W. Newer psychotropic drugs. Current Therapeutic Research, 1963, 5, 40-42.

This editorial suggests reasons for an apparent breakdown of communication between the various groups who are attacking the common problem of understanding and treating the emotions and emotional reactions and suggests how a combined approach may be implemented. Clinical observations of psychotropic drug qualities and development of techniques for identification of the properties in other agents are seen to have taken place largely in fields other than dynamic psychiatry. A schism is traced to a lack of interaction between a "drug-oriented" faction and the dynamic faction; independent developments without providing other groups with pertinent information has been common. Observational techniques of free association, dream analysis, and dynamic interpretation of personality have been infrequently applied in psychopharmacology. As a result, the dynamic psychiatrist is unable to interpret them within the realm of his own knowledge. Similarly, presentations by dynamic psychiatrists seldom include material related to the effect of drugs on the psyche and on the basic psychological elements. It is suggested that the major implementation of a combined approach must occur at the individual level, but societies and journals can be utilized and meetings of both groups can be cross-fertilized. Understanding in both factions can be advanced by continued interaction and by combining their observational methods. An example of good interaction in the early development of the hydrazines is cited.

Section of Clinical Pharmacology
Hahnemann Medical College and Hospital
Philadelphia, Pennsylvania

359 Geocaris, Konstantin, & Ferguson, Anna. The nurse's role in psychiatric out-patient clinics. Journal of Psychiatric Nursing, 1963, 1, 34-40.

As the trend toward psychiatric outpatient clinics evolves, the function of the psychiatric nurse parallels the demands of this rapidly expanding aspect of psychiatric practice. The role of the nurse in drug therapy is becoming more important. Many discharged patients are referred to clinics for followup care while still on maintenance medications. The function of the nurse is to see these patients at frequent intervals and to make observations to detect side effects or other sign posts which alert the doctor to a possible need to change the medication.

(No address)

360 Bowes, H. Angus, & Natarajan, Rangasamy. Office psychopharmacology. Psychosomatics, 1963, 4, 22-26.

Advice on the use of psychopharmacological agents is presented to the general practitioner by the director of an institute of neurology and psychological medicine. Diagnostic indications and contraindications for a wide range of neuroleptic drugs are given. Supportive psychotherapy is outlined for depressive reactions. Dosage ranges are given and are supplemented with the admonition to "titrate the drug against the patient." In addition to this rule, the general practitioner is advised to aim at target symptoms and have patients report side effects immediately. The patient's purse is considered. (6 Refs.)

Institute of Neurology and Psychological Medicine
Grand Forks, North Dakota

361 Gerard, R. W. The nosology of schizophrenia. American Journal of Psychiatry, 1963, 120, 16-29.

An attempt to disentangle the components of schizophrenia was undertaken by giving a wide variety of tests to a number of subject on a longitudinal basis. One hundred schizophrenic and 100 non-schizophrenic male patients were used in special studies and 96 in a pilot run. All together 650 subjects were used for testing. A number of tests and ratings in many areas were explored, including biological, physiological, and psychological. Although the means for the schizophrenic and non-schizophrenic groups did not differ on many measures, the variance in the schizophrenic population was uniformly high. Two biological assay procedures that seem to stand up as discriminators between schizophrenics and non-schizophrenics are the cat optic response and the effects of intraventricular injectio of urinary extracts. The crux of the study was the number and strength of correlations obtained between different measures. There were approximately 100 variables in the psychological area, 75 in the social history area, 70 in psychiatry, 75 in autonomic nervous system and related areas, 40 in biochemical areas, 20 in anthropometry, and 20 involving biological testing. All variables were first intercorrelated with each other within each area, thus approximately squarin the above numbers, and then cross correlated between areas. When each area was considere in relation to the five clinical catagories (paranoid schizophrenia, other schizophrenia uncertain, chronic brain syndrome, other non-schizophrenic), the number and strength of differences in the mean values discriminating these groups was far beyond chance expectation, for some variables as much as 40-fold. Psychological tests alone clearly separated clinical groups. The correlations between psychiatric ratings and psychological measurements were excellent.

University of Michigan
Ann Arbor, Michigan

2 LaVerne, Albert A. (Ed.) Compendium neuropsychopharmacology. Non-barbiturate datives and hypnotics. Journal of Neuro-ychopharmacology, 1963, 4, 345-355.

survey is given of nonbarbiturate seda-ves and hypnotics compiled from various rrent references. The charts provide the neric and trade names of the drugs and e names of their manufacturers. Type and tion of drugs and indications for their e are given, as well as a therapeutic ting in regard to effectiveness and toxi-ty. All side effects, contraindications, d cautions are listed and the recommended sage is tabulated. The variables inherent pharmacological research are responsible r the differences in ratings of therapeutic ficacy. (80 Refs.)

East 82nd Street
w York 28, New York

3 Poldinger, Walter, & Schmidlin, Paul. dex Psychopharmacorum. Bern: Hans Huber, 63, Pp. 1-69.

is is an index of 89 psychoactive drugs in rman, French, and English, which supplies e chemical name, the generic name, and ade name as well as the chemical structures. e list contains substances that have shown lective activity against psychoses, depres-on, and emotional disorders, i.e., tran-ilizers and antidepressants. The arrange-nt follows the headings: neuroleptics ajor tranquilizers), thymoleptics and ymerethics (psychic energizers), and tran-ilizers (minor tranquilizers).

rlag Hans Huber
rn, Switzerland

4 Vukmirovits, Gyorgy. Frenolon. renolon.) Orvosi Hetilap, 1963, 3, 7-268.

enolon (perphenazine + trimethoxybenzoic id) is a new drug produced by the United armaceutical and Food Stuff Factory in ngary. Frenolon was tested on rats and ce. When it was administered i.m., the maximum effect appeared 15 minutes later. Rats stayed alive and gained weight after 10-20 mg/kg of Frenolon administered per os. When it was tested clinically on psychiatric patients, the effect appeared after 2-4 days. Agitation was attenuated gradually, tension was reduced, and pathological hallucinations were less marked. Patients became more organized and more accessible to psycho-therapy. Frenolon was also used on in-patients and ambulatory patients for vegeta-tive disorders, coronary thrombosis, hyper-thyroid, and ulcers. It was also used successfully on children with respiratory and gastrointestinal disorders and agita-tion due to hospitalization. Doses were 1-2 tablets 3 times a day or 1-4 tablets 4 times a day for adults. Side effects were scarce and few. Frenolon was counter-indicated with epilepsy, depression, leuko-penia, and severe kidney and liver damage.

(No address)

365 Berger, F. M. The similarities and differences between meprobamate and barbi-turates. Clinical Pharmacology and Therapeutics, 1963, 4, 209-231.

There are significant differences between meprobamate and the barbiturates, clinically and pharmacologically. This is a review of the literature comparing meprobamate and the barbiturates. The major differences include site and mode of action, effects on conditioned responses and other animal behavior, primary indications for use in human beings, and effects on normal human behavior. The barbiturates are shown to be useful primarily as hypnotics, which in clinical doses, produce motor and intellectual impairment. Meprobamate is shown to be a specific antianxiety agent which produces no significant behavioral impairment at clini-cal dosage. (98 Refs.)

Wallace Laboratories
Cranbury, New Jersey

366 Poldinger, W. Die Besonderheiten des klinischen Wirkungsbildes von Vesitan. (Peculiarities of the clinical aspects of the Vesitan effect.) Therapeutische Umschau, 1963, 20, 68-70.

Vesitan, a combination of thiopropazate and chlorphencyclan, is superior to pure phenothiazine derivatives because of its suppression of parkinsonlike side effects. The author reviews the literature on the components of Vesitan and their individual therapeutic effects, as well as side effects, such as extrapyramidal symptoms. He points out the advantages of a combination of both by stating that a change in dosage does not only cause a quantitative change in results in schizophrenics with autism but also a qualitative one. This consists mainly in its ability to aid in the "remobilization" of chronic schizophrenics. Intravenous application in patients with stupor has successfully replaced the usual treatment with electroshock.

Psychiatric Clinic, St. Urban
Luzern, Switzerland

367 Muller, Christian. Uber psychische Stimulation oder Dampfung bei Sauerstoffmangel und ihre Beziehung zu psychopharmakologischen Problemen. (On psychic stimulation or suppression through lack of oxygen and its relationship to psychopharmacological problems.) Archiv fur Psychiatrie und Zeitschrift fur die gesamte Neurologie, 1963, 204, 199-208.

The reactions to O_2-deficiency can be paralleled to those of neuroleptic drugs in regard to the prevelance of suppressive and depressive effects which they cause. In oxygen-deficiency tests performed on 800 mentally and physically healthy males, ages 20-30, three reactions were observed: a) constant progressive decrease of energy, attention and clarity of thought, followed by apathy, resignation, catatonia and finally unconsciousness; b) a short excitation phase with euphoria, hyperactivity, and slow transition to the final stages of reaction a; and c) constantly increasing euphoria, hyperactivity, lack of judgment and motor excitement followed by a rapid transition to unconsciousness. It is suggested that these differences in reactions are caused by the differences in constitution and development of the subject. The oxygen-deficiency experiments reconfirm the rule, that psychotropic drugs do not influence isolated psychic phenomena, but always cause an enhancement or a reduction of these phenomena within the total behavioral pattern of the subject.

University Psychiatric Clinic
Lausanne, Switzerland

368 Buckert, A., & Niederberger, W. Das Placeboproblem und seine Bedentung fur die Klinische Prufung von Arzneimitteln. (The placebo problem and its importance in the clinical evaluation of drugs.) Schweizerische Medizinische Wochenschrift, 1963, 93, 344-349.

A placebo is a pharmacodynamically inert substance. Earlier, the use of such harmless dummy preparations was confined to physically labile patients demanding drug therapy which the doctor thought superfluous. In recent years, it has become increasingly clear that so-called "placebo effects" play a considerable part, particularly in psychosomatic disturbances. Such effects are by no means always favorable; "placebo side effects" also occur. When clinical trials of drugs are conducted, account must be taken of the possibility that some of the favorable and unfavorable effects observed are attributable to placebo effects. It must also be considered that in many diseases spontaneous improvement supervenes without drug therapy. When trial preparations are being tested, the judicious use of a placebo enables changes due to placebo effects and the spontaneous course of the disease to be distinguished in large measure from the actual pharmacodynamic action of the drug on trial.

Hoffmann LaRoche & Co.
Basel, Switzerland

9 Poldinger, W. Uber die "anti-
ychotische Wirking" verschiedener Psycho-
armaka. (On the "antipsychotic effect"
various psychopharmacological agents.)
erapeutische Umschau, 1963, 20, 143-145.

e author comments on the "antipsychotic"
fects of psychopharmacological drugs as
viewed from the vantage point of the
ychiatrist and that of the pharmacologist.
mparative tests by various researchers
ve shown that, for instance, all pheno-
iazines, which have found use in psycho-
armacology, may have an influence on the
me symptoms. They may have different
ectra of effect and different intensities
effect. Yet, the author suggests that
thin this drug group one may find varia-
ons in the quantities needed, but that the
alitative differences are small.

ychiatric Clinic, St. Urban
zern, Switzerland

0 Rickels, Karl. Psychopharmacologic
ents: a clinical psychiatrist's individual-
tic point of view: patient and doctor
riables. Journal of Nervous and Mental
sease, 1963, 136, 540-549.

idence has increasingly accumulated during
e past several years to support the clini-
l observation that important relationships
ist between patient, as well as physician
riable, and drug response. These variables,
ther by interaction or separately, may over-
me pharmacological drug effects, and depend-
g on the personality characteristics,
titudes and expectations of the patient,
well as the physician, may influence drug
sponse in controlled, as well as uncon-
olled studies. While many of these vari-
les can be evenly distributed by such
thods as randomization of study populations
d by the use of multiple therapists, these
riables contribute strongly to the results
und in drug studies, and will furnish more
aningful data for drug research.

partment of Psychiatry
iversity of Pennsylvania
hool of Medicine
iladelphia, Pennsylvania

371 Imlah, Norman W. Drugs for depression. British Medical Journal, 1963, 5329, 538.

The author claims that hydrazine derivatives are effective in conditions that are resistant to other drugs, but that disbelief in a drug may counteract and even reverse pharmacological effects. He objects to the nihilistic approach to treatment expressed in an earlier article where it was stated that hydrazines are little more effective than placebo. (4 Refs.)

Birmingham 13, England

372 Stephen, P. M. Recent advances in pharmacology. Journal of the Christian Medical Association of India, 1963, 38, 39-44.

The author comments on tranquilizers such as phenothiazines and antidepressives such as MAO inhibitors. He stresses the efforts that have been put forth to produce psychopharmacological drugs that are free of side effects, and that give the patient freedom from his dominant worry or memory and at the same time leave the individual capable of doing his routine duties. Various applications of these drugs are listed besides their uses in psychiatry. Tranquilizers are used as antiemetics and for the treatment of travel sickness; also as premedication agents in anesthesia. Lately they have found a place in treatment of experimental cardiac arrhythmia and experimental epilepsy of animals.

Department of Pharmacology
Christian Medical College
Vellore, S. India

373 Klerman, Gerald, L. Assessing the influence of the hospital milieu upon the effectiveness of psychiatric drug therapy: problems of conceptualization and of research methodology. Journal of Nervous and Mental Disease, 1963, 137, 143-154.

The implications in the relationship between social environment in which the patient is treated and the effectiveness of psychiatric drug therapy are discussed. The finding of

significant drug-milieu inactivation would raise serious doubts as to the generalizing of results derived by double-blind placebo studies in which the environmental factors were not specified. The authors describe four models for possible relationships: 1) Drug effects are independent of the milieu; 2) drug effects are augmented by the milieu; 3) drug effects and milieu factors bear a reciprocal relationship between drugs and environment. Problems of research design, such as the patients' characteristics, patterns of drug prescription and means of assessment of improvement, are also discussed.

Massachusetts Mental Health Center
74 Fenwood Road
Boston, Massachusetts

374 Werboff, Jack, & Gottlieb, Jacques S. Drugs in pregnancy: behavioral teratology. Obstetrical and Gynecological Survey, 1963, 18, 420-423.

The authors review the reports of studies with prenatal administration of psychotropic drugs, alcohol, sedatives, and barbiturates. Drugs that altered the serotonin level were found to be toxic for neonatal survival, and resulted in increased activity, emotionality and audiogenic seizures. Reserpine, chlorpromazine, and meprobamate increased neonatal mortality regardless of the trimester of administration, and affected general growth and development as measured by weight gain. Human data indicate that chlorpromazine and reserpine were implicated in respiratory distress in the newborn, antepartum bleeding and prematurity and infant mortality. The authors admonish practitioners to weigh the immediate benefits of administering a particular drug to a pregnant woman against the possible toxic or delayed behavioral effects of the drug on the offspring. (23 Refs.)

Department of Psychiatry
Wayne State University College of Medicine
Detroit, Michigan

375 Cerletti, A., & Hofmann, A. Mushrooms and toadstools. Lancet, 1963, 7271, 58-59. (Letter)

Small doses (4 mg) of psilocybin or psilocin both isolated from Psilocybe mexicana, generally produce a sense of well being, whereas higher doses (6-12 mg or more) produce profound psychic phenomena associated with altered spatial and temporal perception in addition to a distorted awareness of the self and body image. Concomitant visual stimulation predisposes toward illusions and hallucinations. These substances are currently being explored to ascertain their efficacious application to psychiatric disorders. A synopsis of the historical impact of these compounds prior to their isolation from Mexican mushrooms is also included. (14 Refs.)

Pharmacological Laboratories
Sandoz Ltd.
Basel, Switzerland

376 Lane, Montague (Ed.) Drug therapy. Medical Record and Annals, 1963, 56, 55.

It is recommended that in patients with chronic pain due to fatal disease or whose life expectancy is less than 6 months, short term narcotic therapy be given, and that addiction to these drugs not be a consideration in these cases. Sedatives, tranquilizers, and hypnotics are indicated to provide complete symptomatic treatment.

Baylor University College of Medicine
Houston, Texas

377 Frommer, Eva. The use of drugs. Nursing Times, 1963, 59, 238-240.

The author describes effects of psychotropic drugs such as antidepressants and particularly the MAO inhibitors for the benefit of psychiatric nurses. She describes some of the more frequent side effects and the dosages administered for maintenance. She also stresses the nurse's part in giving the patient the necessary courage to fight mental illness.

(No address)

378 Parhon-Stefanescu, Constanta, Rodin, ., & Arsene, Aurora. Considerations sur a fonction du cortex surrenal dans les aladies psychiques. (Considerations on he suprarenal function in mental illnesses.) nnales Medico-psychologiques, 1963, 121(2), 81-190.

he authors review the literature from 1908 o the present on the relation of the supra-enal functions to mental illness.

No address)

379 Bordeleau, Jean-Marc. Insulintherapie t troubles psychiatriques. (Insulin therapy nd psychiatric disorders.) L'Union Medicale u Canada, 1963, 92, 208-210.

he author comments on insulin treatment for chizophrenics. He statistically analyses he results described in papers which are ited in an annotated bibliography by Miriam R. eller (NIMH). He shows that results indicate o significant differences between a group f schizophrenics treated with deep insulin oma and other groups treated with insulin ubcoma, electroshock, electronarcosis, metra-ol, or psychotherapy. When insulin therapy s compared to chlorpromazine and other euroleptic drugs, the percentage of remis-ions is much higher with psychopharmacologi-al agents.

o address)

380 Cornu, Frederic. Psychopharmakotherapie. Psychopharmacotherapy.) Psychiatrie der egenwart, 1963, I/2, 496-659.

his volume surveys the therapeutic effects, ndications, contraindications and physical ide effects of psychopharmacological agents. europhysiological and biochemical research esults are given. Psycholeptic, psycho-naleptic, and psychodysleptic drugs are iscussed. (911 Refs.)

sychiatrische Universitatklinik aldau, Berne, Switzerland

381 Martin, Gustav J. The biochemical basis of psychotherapeutics. Part III. Journal of the Germantown Hospital, (Philadelphia), 1963, 4, 23-28.

The authors review the literature on the biochemical theories of action of psycho-therapeutic drugs. They conclude that any integrated theory must contain in it an attempt at analysis of intelligence. Since intelligence represents the highest degree of order as informational content, it must correlate with unique four dimensional con-structs. The interplay of enzymes, co-factors, substrates, products, ions, triplex formations, and other interacting components are discussed.

Germantown Hospital
Philadelphia, Pennsylvania

382 Jacobsen, Eric. The clinical pharma-cology of the hallucinogens. Clinical Pharmacology and Therapeutics, 1963, 4, 480-503.

A review of 177 studies in the last 15 years and relevant to the pharmacology of hallucinogenic or psychotomimetic agents is presented, with tables of names, effective human hallucinogenic doses (EHD), and approximate duration of effect of known hallucinogens. For comparison some related compounds without hallucinogenic properties are listed. The history and chemistry of three groups are given: mescaline, lysergic acid, and tryptamine groups. Absorption, distribution, and elimination are discussed; the distribu-tion of lysergide had been determined only in animals using C^{14}-labeling. Clinical effects of the hallucinogens are discussed under two phases which are described as following a latency period: the vegetative phase characterized by subjective disagree-able symptoms and objectively measured re-sults of sympathetic nervous system stimu-lation, and the psychic phase. Principal symptoms of the psychic phase are listed and described as related to dosage, as are the relation of dosage to psychometric per-formance. Human tolerance and cross-toler-and are mentioned in connection with common

properties of the hallucinogens. The influence of hallucinogens on animal behavior is given symptomatically and in relation to multiples of EHD required to change behavior. Peripheral and central effects are presented as are potentiation data in combination with other psychopharmacological agents. In discussing possible sites of action, no definite conclusions are presented though it is suggested that hallucinations are predominately of central origin. Chlorpromazine and other drugs are reviewed as synergists and antagonists to the hallucinogens as is the antagonistic and synergistic action of the latter agents. Hypotheses on the mode of action and the relation of hallucinogens to various psychotic states, principally schizophrenia, are presented. (177 Refs.)

Royal Danish School of Pharmacy
Copenhagen, Denmark

383 Wilson, Ian C., Vernon, J. Taylor, Guin, Thomas, & Sandifer, Myron G., Jr. A controlled study of treatments of depression. Journal of Neuropsychiatry, 1963, 4, 331-337.

A controlled, blind investigation was carried out in two phases over a period of 7 months to evaluate treatments for depression. The subjects were 36 female patients who could be placed in one of the following diagnostic catagories: Manic depressive (depressed type), involutional depression, or depressive reaction. Each patient was assigned by random order to one of four treatments for a period of 5 weeks. The treatments were: ECT-imipramine, ECT-placebo, thiopental-imipramine, and thiopental-placebo. The degree of depression was assessed by the MMPI and the Hamilton Scale. Results showed that the ECT-imipramine groups and the ECT-placebo groups showed the greatest improvement. Because of the possibility of insufficient dosage of imipramine, a second study was undertaken with higher dosage levels. The initial dose was approximately 240 mgs rather than 150 mgs as used in the first phase, and the maintenance dose was higher. In this second phase imipramine was as effective as ECT in relieving the symptoms of depression. Six patients developed behavioral complications, 4 of which were on ECT and imipramine. Almost all patients on imipramine developed some extrapyramidal reactions over 200 mg/day. High doses of imipramine also caused autonomic effects and hypertension. Six patients developed skin rashes. The authors conclude that one would encounter possible complications with both ECT and imipramine, but both are effective in the treatment of depression.

Broughton Hospital
Morgantown, N. C.

384 Halas, Evan J. Comparison of tranquilizers with remotivation groups in the treatment of regressed schizophrenics. Comprehensive Psychiatry, 1963, 4, 126-131.

An attempt was made to compare the therapeutic value of a social approach with that of a pharmacotherapeutic approach using phenothiazines. Two groups of regressed female schizophrenics were selected. For 6 months, one group was exposed to a therapeutic program consisting of the administration of phenothiazines followed by a placebo period and then by a remotivation period without tranquilizers. The order of the therapeutic approaches was reversed in the other group. Remotivation is described as a simple group interaction with structured activity which allows the psychiatric ward nurse to reach her patients in a meaningful and constructive way. The patients were tested prior to and after each period; the Multidimensional Lorr Scale, a remotivation progress report, and clinical judgment based on patient and nurse interviews were employed. Differences between the responses to each approach and the difficulty of obtaining measurements consistent with the clinical picture are discussed. After 6 months, no conclusive results were obtained in favor of either approach. (15 Refs.)

Columbus State Hospital
Columbus, Ohio

385 Maronde, Robert F., Haywood, L. Julian, Feinstein, Donald, & Sobel, Charles. The monoamine oxidase inhibitor, pargyline hydrochloride, and reserpine. Journal of the American Medical Association, 1963, 184, 7-10.

This study presents an evaluation of pargyline hydrochloride (Entonyl) by the double-blind technique, using reserpine-treated patients as controls; observations of a preliminary nature were made concerning the urinary metabolites of reserpine in

these hypertensive patients. Patients who had attended a hypertension clinic for at least 6 months were placed into three treatment groups by dispensing in sequence: 1) active reserpine and placebo tables, 2) active reserpine and active pargyline HCl tablets, and 3) active pargyline HCl and placebo tablets. Use of the nonhydrazine monoamine oxidase inhibitor, pargyline HCl, resulted in a significant lowering of standing patients' blood pressure but there was little effect on supine pressure. Oral reserpine in the dose of 0.5 mg/day had little effect upon hypertensive blood pressure levels during a 12-week period and had no effect on the antihypertensive action of pargyline HCl. Methyl reserpate found in the urine of patients who received oral reserpine suggested inactivation by hydrolysis in the intestine. Results are compared with those found earlier using guanethidine sulfate and methyldopa.

2025 Zonal Avenue
Los Angeles 33, California

386 Nussbaum, Kurt, Wittig, Barbara A., Hamlon, Thomas E., & Kurland, Albert A. Intravenous nialamide in the treatment of depressed female patients. Comprehensive Psychiatry, 1963, 4, 105-116.

As observed by previous investigators, nialamide can safely be given intravenously in large doses with minimal side effects. However, the expectation that this method might accelerate or increase the drug efficacy in depressive reactions has not been supported. On 4 consecutive days, 30 white depressed female patients were randomly assigned to double-blind intravenous nialamide (500-750 mg) or placebo treatment, administered in infusions of 1000 cc of 5 percent glucose in normal saline. The 16 drug and 14 placebo patients were evaluated before and after treatment and at the end of a 10-day followup period during which most patients received oral nialamide. Laboratory examinations, as well as various psychopathological parameters, were used to determine criteria of change. These parameters were 1) a global psychiatric evaluation of change in the areas of behavior, affect, thinking, and physical complaints; 2) a global depression score obtained by summing up the 4-point scales of certain target symptoms; 3) the Beck Depression Inventory; and 4) the Minnesota Multiphasic Personality Inventory (MMPI). The evaluation provided the data for the analysis of differential treatment effectiveness. Contrary to previous findings, no differential treatment effects were noted.

Research Department
Spring Grove State Hospital
Baltimore, Maryland

387 Hamilton, M., Hordern, A., Waldrop, F.N., & Lofft, J. A controlled trial on the value of prochlorperazine, trifluoperazine, and intensive group treatment. British Journal of Psychiatry, 1963, 109, 510-522.

Prochlorperazine, trifluoperazine, a placebo and intensive social and nursing treatment were compared by themselves and in combinations on 63 male and 63 female chronic schizophrenic patients. Statistical analysis shows that both drugs were effective and that "moral treatment" helped reduce symptoms on male but not female patients. Chronic deteriorated schizophrenics, average age of 46, were divided into groups which received PCP, TFP, or placebo for 3 weeks. PCP plus moral treatment, PCP plus routine care, TFP plus moral treatment, and TFP plus routine care were given through the 17th week. Though both drugs were effective in the doses given (PCP range of daily dose 20-160 mg, and TFP average range of daily dose 7-80 mg), trifluoperazine was more so, but also had more severe side effects. These comprised parkinsonism, akathisia, dyskinesia, and drowsiness. Most of the improvement took place by the third week and there was little change after that. Occupational, recreational group therapy, and special nursing care reduced symptoms in male patients but not in female. In male schizophrenics, the degree of improvement was similar for all types of treatment given, such as the two drugs alone, "moral" treatment alone or the two categories combined. In women, a moderate improvement du to PCP was enhanced by "moral" treatment. TF was more effective in women when used on its own but had an inhibitory effect when used wi the other types of therapy.

Stanley Royd Hospital
Wakefield, England

388 Simon, Werner, & Hopkins, Wendell G. Treatment of schizophrenia with potassium and magnesium aspartates (Spartase). Comprehensive Psychiatry, 1963, 4, 62-63.

Empirical treatment with potassium and magnesium aspartates in two schizophrenic patients failed to produce clinical improvement. Biochemical and hemologic studies with pyruvic and lactic acid reveal their involvement in metabolic cycles in the human which influence energy and fatigue. Responding to the findings by Beckett and coworkers that an elevated lactate pyruvate ratio is present in schizophrenic patients, the authors seek to correlate the anergic symptoms found in schizophrenia with increased serum pyruvate and lactic levels. They proceed to do this by administering potassium and magnesium aspartates to two schizophrenic patients. The aspartates are recommended agents in the treatment of fatigue states and it has been shown that they delay the rise of serum pyruvate and lactic acid levels in rats which undergo strenuous exertion. One patient was given the aspartates (Spartase) 1000 mg b.i.d. for 1 week, the other 1000 mg b.i.d. for 1 month with no clinical improvement observed. No attempt was made to expand this study to include a great sampling of patients in a preferable double-blind controlled study. Serum lactate and pyruvate level determinations were not part of this limited study.

Veterans Administration Hospital
Minneapolis, Minnesota

389 Angst, J. Vergleich der antidepressiven Eigenschaften von Amitriptylin und Imipramin.(Comparison of the antidepressive qualities of amitriptyline and imipramine) Psychopharmacologia, 1963, 4, 389-401.

A comparison between amitriptyline and imipramine showed that while both have good results in hypochondriac depressive syndromes, amitriptyline is superior in agitated endogenous depressions and inferior in inhibited anergic and anxious depressive syndromes. Amitriptyline was given to 100 depressed patients, i.m. or orally in doses of 50-75 mg per day in the first 20 patients and 150-200 mg in the rest of the patients. Treatment lasted from one to several weeks. The doses of imipramine administered to 200 depressed patients are not recorded. Amitriptyline was more effective in patients with endogenous depressions who had first attacks. In repeated attacks the response decreased. The slightly neuroleptic action of this drug was especially helpful in those with depressive tension and sleep disorders. The advantage of amitriptyline seemed to be that it is better tolerated, which is particularly important with outpatients. The optimal dose was 150-200 mg per day. Side effects were less frequent and less severe than with imipramine. Among them were dryness of mouth, thirst, tremor, excessive perspiration, hypokinesia, euphoria, restlessness, and agitation. Some cases resistant to amitriptyline responded to imipramine, desipramine, thioridazine, or electroshock. Followup studies showed that after 3 months, 80 percent of the successes continued after cessation of treatment. In 50 percent of those patients resistant to the drug other antidepressant treatment effected cures within 3 months. (21 Refs.)

Psychiatrische Universitats Klinik
Burgholzli, Zurich, Switzerland

390 Sanchez Pena, Carlos Jerjes. Neuvas armas terapeuticas. Trastornos psicovegetativos cardiovasculares. Su control con Insidon. (New therapeutic weapons. Psychovegetative cardiovascular disorders, their control with Insidon.) Prensa Medica Mexicana, 1963, 28, 44-46.

Insidon was found very satisfactory in controlling psychovegetative cardiovascular disorders. Out of 47 patients (31 females and 16 males), 15-70 years old, 14 patients had cardiopathies, whereas 33 had normal cardiovascular systems. All patients had emotional and neurovegetative (autonomic nervous system) disorders, with anxiety, restlessness, fear, insomnia, tachycardia, headache, motion sickness, abdominal fullness, tremor, and sialorrhea. Patients were administered per os a 50-mg tablet of Insidon with each meal (3 tablets a day) for 14 days to 1 month. Dosage varied

in some cases. Patients were examined regularly. The results of Insidon on mental and neurovegetative systems were as follows: excellent, good, or moderate results in 37 patients, unsatisfactory results in 10 patients. There were minimal side effects such as somnolence (1 case) and dryness of the mouth (3 cases).

Vera Cruz
Ver., Mexico

391 Lopez de Nava, Alfredo. Tension y ansiedad en ginecologia. Consideraciones sobre su tratamiento con flufenazina.(Tension and anxiety in gynecology. Remarks on their treatment with fluphenazine) Prensa Medica Mexicana, 1963, 28, 54-56.

Fluphenazine was satisfactory in treating tension and anxiety in gynecology. Out of 21 ambulatory females (18-59 years; average: 38 years), tension and anxiety were associated with gynecological aspect in 18 cases and with nonphysical aspect in 3 cases. Tension and anxiety had been present for 2 months to 6 years (average: 10 months); 1-2 mg of fluphenazine were administered per 24 hours in a single dose or, in case of intolerance, in a fractional dose. Patients were examined at 10-day intervals. Depending on results, dosage varied or treatment was suspended. Slight somnolence was the only side effect. Therapeutic results were rapid and sustained.

Jefe del Servicio Genecologia y Obstetriacia
Hospital Central de Marina, Mexico

392 Kröger, Robert. Die Behandlung psychischer Erkrankungen mit Vesitan.(Treatment of psychic disorders with Vesitan.) Medizinische Welt, 1963, 8, 440-444.

Vesitan, a combination of thiopropazate and a piperazinyl derivative, was effective in schizophrenics, alcoholics with delirium, and those with paranoid-hallucinatory syndrome, catatonic stupor, and depressions. A group of 106 women of all ages was treated for 35 days with 30-100 mg per diem of Vesitan. Route of administration was intramuscular or intravenous and subsequently oral. Ninety-five percent of the women were benefited by the treatment and 63 (60 percen of these could be released from the hospital Ten percent of the group did not respond. Among the side effects were extrapyramidal symptoms in 26 percent, irritations of the autonomic nervous system in 20 percent, cardiovascular disturbances in 16 percent, and skin disorders in 3 percent. Blood and liver functions were normal. The author fee that this drug is not only helpful in the treatment of inpatients, but because of its moderate side effects, well suited for outpatients also.

Oldenburgisches Landeskrankenhaus
Wehnen, 2901 Post Ofen, Germany

393 Anton, A. Gamaquil(gamma-Phenylpropyl carbamat) in der nervenärztliehen Praxis. (Gamaquil (gamma-phenylpropylcarbamate) in neurological practice.) Medizinische Welt, 1963, 12, 642.

Gamaquil (gamma-phenylpropylcarbamate) showed good therapeutic results in muscle rheumatism, neuroses of organic origin, and vegetative depressions. It has been beneficial as an analgesic muscle relaxant. In 24 cases of vegetative depressions, symptoms were relieved or eliminated completely, 2 to 4 weeks after onset of treatment. Rate of administration was 2 tablets t.i.d. initiall and was reduced later to 1 tablet t.i.d. Side effects were dependent on dosage. One of them, fatigue, usually disappeared after the patient had been treated with the drug for a certain period of time.

(No address)

394 Engelmann, Gerhart. Beitragzur Angina pectoris-Therapie mittels Monoamine-oxydase-Hemmern.(Contribution to the therapy of angina pectoris by means of MAO inhibitors.) Medizinische Welt, 1963, 5, 280-283.

A combination of phenelzine and PETN (pentaerythrittetranitrate) sometimes in conjunction with phenobarbital, was beneficial in almost all of 200 patients with angina pectoris syndrome. Side effects were of short duration and were not intense.

All patients treated with the drug combination were at the same time on a basic therapy including diet and therapeutic baths. They also had had previous treatments with sedative, spasmolytic, and vasodilating drugs. The optimum dose was 7.5 mg phenelzine (beta-phenylethylhydrazine) and 20 mg PETN, which was administered in tablet form, one tablet t.i.d. or in a few cases, 2 tablets t.i.d. Eighty percent of the patients showed definite relief and freedom from symptoms. The drug was especially helpful in cases of severe coronary insufficiency. Side effects included restlessness, insomnia, dizziness, and gastrointestinal disturbances in five patients, and hyperhidrosis, edema, and color blindness in three patients.

(No address)

395 Flegel, H. Klinische Schizophreniebehandlung mit Haloperidon im katamnestischen Ruckblick. (Catamnestic review of the clinical treatment of schizophrenia with haloperidol.) Symposium Internazionale Sull'Haloperidol E Triperidol, 1962, 367-375.

A study of the catamneses of 120 chronic schizophrenics treated with haloperidol revealed that one-half of the 46 patients released from the hospital had relapses within 9-35 months. Most of the relapses occurred because of the discontinuation of the recommended haloperidol therapy after the patients returned to their homes. In a few cases symptoms reappeared even when patients had continued the therapy for 8 to 18 months. Clinical experience also showed that premedicative symptomatology reappeared when haloperidol treatment was interrupted for 1-2 months. To get reliable results of the catamnesis study, the maximal intervals between recurrence of symptoms were tablulated and statistically evaluated.

Rheinischen Landeskrankenhaus
Dusseldorf, Germany

396 Peters, Uive H. Chronische Methyprylon-Intoxikation und ihre Psychopathologie. (Chronic methyprylon intoxication and its psychopathology.) Archiv fur Psychiatrie und Zeitschrift f. d. ges. Neurologie, 1963, 204, 342-348.

Methyprylon combined with beer caused a symptomatic psychosis in a 50-year-old male, afflicted with Bekhterev's disease (ankylosing spondylitis). The patient had taken 2.0 methyprylon, a nonbarbiturate hypnotic for 8 months in doses of 1.0 t.i.d., combined with a bottle of beer. Two days after a last accidental overdose, he showed signs of psychosis, which expressed itself in extreme clarity of thought, richness of ideas, and increased learning capability. He finally went into a state of anxiety and motor excitement combined with optical and auditory hallucinations. On the fourth day, he fell into a deep sleep from which he awakened with some memory of the events of the last days but apparently free of all symptoms of drug addiction. Since this is the only case of this type reported, no major conclusions can be drawn. It is suggested that there is a certain danger of addiction to methyprylon when taken in combination with beer.

Psychiatrische und Nervenklinik der
Universitat
Kiel, Germany

397 Boittelle,Georges, Boittelle-Lentulo, Claudine, Cophignon, Jeanine, Blotnikas, Gerard, & Thomas, Jacques. Une nouvelle drogue a action antidepressive, le Rd 292. (A new drug with antidepressant action, Rd 292.) Annales Medico Psychologiques, 1963, 2, 86-89.

Rd 292, a new drug with antidepressant action, was beneficial at daily doses of 250-300 mg (oral or i.m.) in 45 patients (male and female) with depressions, schizophrenia, or mental imbalance. This drug is an analog in structure to phenaglycodol, yet it differs in action, since it is not only a stimulant but also an antidepressant. There

were very few side effects, when clinically tested. The most frequent ones were sleep disorders, which were transitory. Electrocardiogram and blood tests were almost always normal. One of the main advantages of Rd 292 is that its favorable action begins at the end of the first week of treatment.

(No address)

398 Monnerot, E., & Barré, R. Chimiothérapie: une butyrophénone, le 2028 M.D. (Chemotherapy: a butyrophenone, 2028 M.D.) Annales Médico-Psychologiques, 1963, 121, 288-289.

A butyrophenone, 2028 M.D., has been found beneficial in patients with agitation in any of its forms because of its symptomatic sedative effect. In 50 cases treated with this drug at a daily dose of 60-80 mg, the authors observed symptomatic relief but could not obtain convincing long-term results in patients with chronic psychoses. It seemed to be helpful in conjunction with other psychotropic drugs in cases of retardation or where grave character disorders, delirium, or dementia was present. Side effects were noticed in 13 of the 50 patients. The most frequent ones were extrapyramidal symptoms. The drug seems to be contraindicated in patients with previous vasomotor disorders.

(No address)

399 Döhner, W., & Eckmann, F. Zur Behandlung paranoid-halluzinatorischer Syndrome mit einem neuen neuroleptischen Kombinationspraparat. (Treatment of paranoid-hallucinatory syndromes with a new neuroleptic combination compound.) Medizinische Klinik, 1963, 1, 24-25.

Vesitan, a combination of piperazynyl-phenothiazine and a CNS-stimulant--chlorphencyclan, was effective in the treatment of acute paranoid-hallucinatory episodes in schizophrenics. The 29 male patients, ages 23-39, who were observed had all the same characteristics. They were schizophrenics of athletic build and were introvert with a tendency to irascibility. In 23 of these patients, a Kipp-effect was noted within 5 to 8 days after treatment with Vesitan was begun. The Kipp-effect is a suddenly appearing change in personality. The patient disassociates himself completely from his earlier thoughts and moods and often cannot recall his former state of mind. Therapeutic doses consisted of 2 ml b.i.d. parenterally plus one tablet, with an additional tablet every day up to the third to seventh day of treatment, when injections were replaced by tablets also. The maximum dose was 140 mg per diem, while the average dose was 80 to 100 mg per diem for 2 to 3 months. Chlorphencyclan is credited with the control of extrapyramidal symptoms caused by the thiopropazate.

(No address)

400 Eckmann, F. Zur Behandlung neuroleptisch bedingter grobmotorisch-extrapyridaler Syndrome. (On the treatment of gross motor extrapyramidal syndromes caused by neuroleptic drugs.) Therapie der Gegenwart, 1963, 3, 349-356.

Akineton, a piperidino-phenylbicycloheptenylpropanol, is considered to be highly effective in the treatment of gross motor extrapyramidal symptoms, caused by neuroleptic drugs because of its wide spectrum of pharmacological effectiveness and its few clinical side effects. The authors have tested this drug for 5 years and have used it successfully in 47 male patients who, out of a group of 1,410, developed dyskinesia and other similar reactions after treatment with neuroleptic drugs. The drug's effect is based on its anticholinergic myospasmolytic, and ganglioplegic action. Besides dyskinesia, akathisia and tremors were also controlled by oral or intramuscular administration within a few hours to 2 weeks' time. Injections were administered 0.005 g/ml b.i.d. Oral dosage consisted of one-half to one tablet, 0.002 g t.i.d. Side effects included dizziness, malaise, vomiting, sleep disturbances, dryness of mouth,

onstipation, and diarrhea. No liver dis-
unctions were observed at any time and
lood, as well as urine analysis, showed no
eviations from the normal.

No address)

401 Flegel, Horst, & Neller, Klaus.
ur Dipiperon-Behandlung chronisch Schizo-
hrener mit Kontroll Vergleichzwischen
ra- und permedikativen Individualver-
äufen.(On dipiperon treatment of chronic
chizophrenics with control comparisons
efore and during treatment in individual
ourses of disease.) Der Nervenarzt, 1963,
4, 85-89.

ipiperon's beneficial effect on chronic
chizophrenics consists predominantly of
eutralizing, harmonizing, and raising their
sychoenergetic level. Its side effects are
imilar to those of other neuroleptica and
an be minimized by a careful dosage in-
rease. A group of 90 chronic schizophrenics
as given daily doses of 120, 240, or 360
g of dipiperon. A statistical evaluation
f the improvement of symptoms as well as
ischarge and readmission rates of the
atients was undertaken and a collective
omparison quotient was derived. Of the 90
atients, 64 could be released, most of
hem in the third month of treatment. Of
he first 43 released after 5 weeks of
reatment, 8 suffered relapses after 3 to
months, 50 patients showed a more even
ersonality, and 40 were more alert than
efore treatment. Side effects included
xtrapyramidal symptoms, tremors, restless-
ess, tachycardia, sleep disorders, skin
ashes, edema, cardiovascular and urinary
isturbances, and blurring of vision. Liver
unction was not affected by the drug.

Rheinischen Landeskrankenhaus
Düsseldorf, Germany

402 Clark, Mervin L., Ray, Thomas, &
Ragland, Robert E. Chlorpromazine in chronic
schizophrenic women: rate of onset and rate
of dissipation of drug effects. Psycho-
somatic Medicine, 1963, 25, 212-217.

There is a lag of 8-16 weeks between
beginning treatment with chlorpromazine and
the appearance of firm, statistically sig-
nificant effects on variables capable of
reflecting drug effects in the observed
period of time. A group of 57 chronic schizo-
phrenic women, ages 25-50, and hospitalized
for more than 5 years was divided into 3
groups and given chlorpromazine (800 mg per
diem), phenobarbital (480 mg), and placebo
capsules. A reduction of the dosage was
followed by complete withdrawal of all
drugs. Ward behavior and intellectual and
psychomotor effectiveness were measured at
certain intervals up to the 56th week after
withdrawal. It appears that higher drug
doses are likely to impair performance early
and that optimal drug effects may be more
quickly reached with lower dosage levels.
Significant lags, measurable in months
rather than days or weeks, were found in the
appearance and disappearance of drug effects.

Department of Medicine and Psychiatry
University of Oklahoma Medical Center
Oklahoma City, Oklahoma

403 Oltman, Jane E., & Friedman, Samuel.
Preliminary investigation of piperacetazine.
American Journal of Psychiatry, 1963, 119,
888-889.

Piperacetazine (Quide), a new phenothiazine
derivative, is an effective agent in
appropriate, selected cases of schizophrenia.
Side effects were minimal. The drug was
administered to 50 female schizophrenics,
ages ranging from less than 20 up to 60.
Dosage was initiated with 10 mg t.i.d.,
and increased up to 30 mg t.i.d. Medica-
tion was maintained from 3 to 20 weeks.
Some 42 percent showed good or excellent
improvement, 58 percent showed insignificant
improvement. Satisfactory results were
obtained mostly in patients with innately
favorable prognostic features. Side effects
were mild and infrequent. They consisted

of sleep disorders, slight dizziness, and one case of mild akathisia.

Fairfield State Hospital
Newtown, Connecticut

404 Rogers, Norman R. Trifluoperazine as a "mobilizing agent" in chronic withdrawn schizophrenics. Diseases of the Nervous System, 1963, 24, 162-166.

Trifluoperazine mobilizes or activates chronic regressed and withdrawn patients. A group of 40 chronic schizophrenic patients, whose case histories are given in an appendix, was treated with trifluoperazine, 5-40 mg for 12-26 months. They had been consistent treatment failures on drug and somatic therapy. On receiving the drug, 21 patients (52.5 percent) showed considerable improvement, 13, while less impressive, had moderate improvement, and 9 patients did not improve at all.

Agnews State Hospital
San Jose, California

405 Howard, Frank M., Jr. A new and effective drug in the treatment of the stiff-man syndrome: preliminary report. Proceedings of the Staff Meetings of the Mayo Clinic, 1963, 38, 203-212.

Case histories of three patients with stiff-man syndrome are presented. Two of the patients responded promptly and dramatically to the administration of diazepam (60 mg daily, divided into 4 or 5 doses). The other patient had some softening of the muscles, but he did not improve functionally. Although the etiology of this syndrome is unknown and the site of action of the drug has not been defined, it appears to be effective in treating a syndrome previously refractory to treatment. One patient became drowsy and unsteady when taking 40 mg daily and it was necessary to reduce his dosage, but no major toxicity was observed.

Section of Neurology, Mayo Clinic
Rochester, Minnesota

406 Kebe, Sara R. ACTH and a chelating agent for schizophrenia. Western Medicine, 1963, 4, 46-48.

Twenty schizophrenic female patients, free of renal disease, were treated with calcium disodium ethylenediamine tetraacetate, a chelating agent, with ACTH. The patients were evaluated before treatment and each day for the five treatment days on a symptom check sheet. Ten patients received the chelating agent and ACTH and 10 received a placebo and ACTH. Nine patients improved (7 drug - 2 placebo), 2 slightly improved (2 drug), and 9 were unimproved (1 drug - 8 placebo). No side effects were observed. In the improved group, calcium desodium ethylenediamine tetraacetate and ACTH had a definite antihallucinatory effect.

Camarillo State Hospital
Camarillo, California

407 Stanfield, Clyde E. Clinical evaluation of diazepam in psychiatric disorders. Southwestern Medicine, 1963, 44, 475-476.

Diazepam appears to be highly useful in anxiety-depression-tension syndromes. It has fewer side effects and less cumulative effects than chlordiazepoxide and other effective psychotropic agents. A group of 46 females and 12 males, ages 19-78, who had had poor responses or adverse reactions to various drugs or other treatment procedure was given diazepam from 5 days to 6 months. Dosage was 5 mg to 40 mg b.i.d. or t.i.d. Concurrent therapy in 19 patients included amitriptyline, methylphenidate, etryptamine, chlorpromazine, promazine and others. In 17.2 percent of the patients, response was excellent, in 53.4 percent good, in 17.2 percent fair, and in 12.1 percent poor. Side effects consisted of drowsiness in seven patients, drowsiness and dizziness in one, and nightmares suffered by one.

415 Medical Center Building
3705 East Colfax Avenue
Denver, Colorado

408 Sotelo, Delfor, Smith, S. Wayne, & Palmer, Beth. Fluphenazine for chronic psychotic patients. Western Medicine, 1963, , 90-91.

group of 30 hospitalized psychiatric atients were maintained on fluphenazine or 90 days with notable success. The atients, ages 32-70, received doses of -30 mg daily. Sixteen patients (53.3 per- ent) showed definite improvement, 13 43.3 percent) remained the same, and 1 ecame worse. Hallucinatory symptoms mproved in 12 and delusions improved in 8. ide effects, in the form of extrapyramidal ymptoms, were noted in 11 patients. Blood, rine, and liver function remained unaltered. luphenazine, a phenothiazine derivative, is aid to be about 25 times as potent clinically s chlorpromazine in both chronic and acute orms of mental disease.

tate Hospital South
lackfoot, Idaho

409 Grant, George H. Chlordiazepoxide sed for apprehensive dental patients: reliminary observations. The Journal of he American Dental Association, 1963, 6, 44-47.

group of 56 male and female dental patients, anging in age from 5 to 50, was given 5 to 5 mg of chlordiazepoxide an hour before reatment to alleviate anxiety and appre- ension. A 10 mg dose was given as well as n the night before treatment. Responses ere excellent in 46 patients and good in 8. wo failed to show beneficial effects of the rug. Chlordiazepoxide appears to be a safe nd effective agent to relax the patient and llay his anxiety, fear reactions, and esistance to dental treatment.

1 Chester Drive
ye, New York

410 Destounis, Nicholas. Enuresis and imipramine. The American Journal of Psychiatry, 1963, 119, 893.

A 15-year-old boy suffering from enuresis accompanied by depression and suicidal preoccupation was put on 50 mg imipramine. Bedwetting ceased and the depression disappeared within a week. Supportive psychotherapy was given and after 2 months he not only was free of the previous symptoms, but became a better student with an optimistic attitude toward the future.

6209 University Avenue
Halifax, Nova Scotia, Canada

411 Karabanow, Oscar. Clinical experience with chlorprothixene in psychiatric syndromes. Applied Therapeutics, 1963, 5, 133-136.

A group of 28 patients with acute brain syndrome due to acute alcoholism and a group of 186 patients with depression, when treated with chlorprothixene showed alteration of the intrapsychic tension, diminution and/or disappearance of subjective symptomatology of anxiety, and rapid compensation of the repressive ego defenses. In the first group of patients, ages 21 to 55, the drug was given in doses of 50-75 mg i.m. followed by 50 mg q.i.d. per os. Ten of these patients received an additional 50 mg daily. The second group received 200-300 mg/day i.m. followed by oral administration. The response to therapy was in all 28 cases excellent. In the remaining 186, response was excellent in 69, very good in 46, and good in 53. Eighteen were considered failures. Side effects consisted of dizziness, drowsiness, hypotension, constipation, and tremor. These were easily controlled by dosage reduction.

Institute of Psychotherapy
Kingston, Ontario, Canada

412 Rudolf, G. de M. The treatment of spasticity with chlordiazepoxide (Librium). British Journal of Psychiatry, 1963, 109, 544-547.

A group of 14 severely subnormal patients with spasticity was given chlordiazepoxide, 5 mg t.i.d. initially,rising to 10 mg t.i.d. Improvement in gait was noted and cessation of tachycardia, which had developed on an initial dose of 15 mg t.i.d. Improvement often began a considerable time after commencement of treatment. In those patients who were for a greater length of time on a higher dosage, no relapse recurred after cessation of drug treatment. The author also reviews the literature of the use of some other relaxants in spasticity.

(No address)

413 Janecek, James, Schiele, Burtrum C., Bellville, Titus, & Anderson, Richard. The effects of withdrawal of trifluoperazine on patients maintained on the combination of tranylcypromine and trifluoperazine: a double-blind study. Current Therapeutic Research, 1963, 5, 608-615.

A study of 30 psychotic and neurotic patients revealed that the combination of 10 mg tranylcypromine and 1 mg trifluoperazine 1) controls target symptoms; 2) is more efficacious than tranylcypromine alone; and 3) does not have greater untoward effects than tranylcypromine alone. The patients were divided in two groups, one receiving the combination, one receiving tranylcypromine only. They had been diagnosed as depressive reaction, manic depressive, schizophrenic reaction, sociopathic personality, passive-aggressive personality. The duration of the test was 4 weeks, with early termination necessary in a few patients, whose condition worsened. Psychological evaluation was performed throughout the study. Side effects included drowsiness, overstimulation, motor restlessness, sleep disorders, dry mouth, dizziness, syncope and blurred vision. Untoward effects of one agent are not potentiated by the other.

University of Minnesota
Minneapolis, Minnesota

414 Dierks, M. A comparison of two phenothiazines in the treatment of schizophrenics. American Journal of Psychiatry, 1963, 119, 775-776.

Trifluoperazine and thioridazine showed the same degree of tranquilizing effect in 109 hospitalized female schizophrenics, ages 23-60. Extrapyramidal symptoms were induced by thioridazine in 1 patient and by trifluoperazine in 79 patients. The diagnoses were schizophrenic reaction, involutional psychoses, and manic-depressive reactions Benztropine had to be added to trifluoperazine to control the parkinsonian phenomena. Range of daily dosage was 4-40 mg for trifluoperazine and 50-800 mg for thioridazine.

(No address)

415 Edlinger, E. Zur Prämedikation in der Kinderanesthesie. (On premedication in anesthesia of children.) Der Anaesthesist, 1963, 12, 174-178.

The problems of premedication in children are discussed. The danger that induction of anesthesia acts as a psychic trauma and by this interferes markedly with the emotional stability and the subsequent behavior of the child is of particular importance. The vital functions of respiration and circulation have to be considered as well. With this as criteria, Itridal was evaluated for its suitability. The drug has proved to be very satisfactory and reliable for premedication in children provided that the chosen doses are administered i.m. at least 30 minutes before induction. The children do not resist induction. Respiration is not depressed. There is only a statistically insignificant fall of arterial pressure and an increase of pulse rate, not

exceeding 5 percent, which is of no practical consequence.

Anaesthesiceabterlung der Cherurgischen
Universitätsklinik
Graz, Austria

416 Gosselin, Jean-Yves. Essai clinique du LA-111. (Clinical test of LA-111.) L'Union Med. du Canada, 1963, 92, 335-338.

In the clinical evaluation of LA-111 over 106 patients, the new anxiolytic drug seemed to be mostly active in the neurotic reactions and the psychosomatic syndromes. The epilectic and schizophrenic patients presented an improvement in communicating their problems and in their social attitude. In some severe neuroses and schizo-affective reactions, the authors obtained good results. A few side effects were observed among the patients receiving more than 10 mg a day, but no severe toxic reactions were noted.

L'Hopital St. Michel-Archange et a l'Hopital
du Saint-Sacremend,
Quebec, Canada

417 Borenstein, P., Bles, G., Dabbah, M., & Croize, B. Un nouveau correctcur des syndromes extra-pyramidaux induits par les neuroleptiques: l'ethybenzatropine(UK 738). (A new corrector of extrapyramidal symptoms induced by neuroleptic drugs: ethybenzatropine (UK 738).) Psychiatria et Neurologia, 1963, 145, 144-179.

Based on the results of pharmacological investigations, a clinical trial has been made of ethybenzatropine (UK 738), a synthetic tropane derivative which relieves the extrapyramidal disorders elicited by neuroleptics. The authors gave 115 courses of treatment including 77 under neuroleptic therapy, the total amounting to 3,700 days of treatment. In addition, EEG studies were made in 84 cases. Ethybenzatropine, given parenterally (4-8 mg i.v. or 5-15 mg i.m. daily) and then orally (15-30 mg daily), controlled both the early paroxysmal excitotonic states (in all cases) and the parkinsonlike symptoms (in almost 90 percent of cases). This double therapeutic effectiveness is regarded by the authors as the markedly unique feature of the product. Ethybenzatropine, in addition, exerted a clearcut anxiolytic effect without impairing the effect of the neuroleptics and relieved, to a certain extent, secondary psychomotor inhibition. The drug was also effective in organic extrapyramidal syndromes (chorea, parkinsonism). Side effects, related to the drug's atropinelike actions, were infrequent and, on the whole, moderate or mild. There was no pain at the site of injection and no gastric irritation following oral administration. Ethybenzatropine exerted an "activating" effect on the EEG of epileptic subjects in almost half the cases but aggravated the clinical condition only in isolated instances.

Hopital Psychiatrique de Villejuif
Seine, France

418 Van Praag, H. M., & Leijnse, B. Die Bedeutung der Monoaminoxydasehemmung als antidepressives Prinzip I. (The importance of MAO-inhibition as an antidepressive principle. I.) Psychopharmacologia, 1963, 4, 1-14.

The MAO-inhibiting hydrazines are effective exclusively in the treatment of depressions of predominantly vital coloration. A depression was considered to be of "predominately vital coloration," if the complete series of the following symptoms were found: unmotivated depression experienced as "leibesnah"; retardation of thoughts and actions; reduced receptiveness to psychical feelings; disturbances in conception of time and somatic disorders. Within the scope of an investigation into the significance of MAO-inhibition regarding the antidepressive effect of these drugs, their influence on the breakdown of endogenous serotonin was studied in 23 patients. No influence was demonstrated; this means that no such degree of MAO-inhibition is reached as to result in a demonstrable general MAO-deficiency. ECT--with a range of indication corresponding with that of the

antidepressive hydrazines -- did not influence general MAO activity either. Depressive patients with a complete vital syndrome who appeared to be therapeutically accessible to MAO-inhibitors excreted significantly less 5-HIAA before treatment than similar patients who are resistant to these drugs or normal control subjects. The level of excretion showed normalization synchronous with vital recovery. The possible causes of this phenomenon were discussed. The theoretical significance of this phenomenon is two-fold: 1) It suggests that the pathology of vitality is more complex than is generally assumed. 2) It demonstrates the necessity of more refined nosological and syndromal classification of psychopathological manifestations for psychopharmacological investigation.

Psychiatrische Klinik
Kranskenhaus Digkzigt
Rotterdam, Holland

419 Poldinger, W. Laroxyl (Amitriptylin), ein Thymolepticum mit neuroleptischer Wirkungscomponente. (Laroxyl (Amitriptyline), a thymoleptic drug with a psychopharmacological action component.) Der Nervenarzt, 1963, 34, 80-84.

Amitriptyline is beneficial in the treatment of depressions in schizophrenic patients, although it occasionally causes acute psychotic side effects. These side effects are too severe to be risked in agitated schizophrenics. Tests with 102 schizophrenics indicate that this drug which is chemically comparable to imipramine and chlorprothizene, combines a "thymoleptic" effect with a psychopharmacological effect. To avoid delirium and confusion in patients, it is recommended that amitriptyline be combined with chlordiazepoxide.

Kantonalen Psychiatreschen Klinik
St. Urban, Luzern, Switzerland

420 Angst, J., & Poldinger, W. Klinische Erfahrungen mit dem Butyrophenonderivat Methylperidol (Luvatren). (Clinical experiences with butyrophenon derivative, methylperidol (Luvatren).) Praxis, 1963, 44, 1-20.

Methylperidol seems to be beneficial in cases of paranoid schizophrenia with hallucinations. A group of 122 patients, of whom 101 were schizophrenics, was given 12-30 mg of the drug i.m. or orally for a period of from 1 week to 6 months. The drug proved to be less effective than chlorpromazine and reserpine. Its side effects included dyskinesia, akathisia, tremors, tiredness, dizziness, hypersalivation, diarrhea, nausea, vomiting, and allergies.

Psychiatrische Universitatsklinik
Burgholzli, Leonggstr. 31
Zurich 8, Switzerland

421 Trebesses, M. G. Utilisation in obstetrique d'unpsycholeptique: le Dominal. (Obstetrical use of a psycholeptic drug: Dominal.) Journal de Medicine de Bordeaux, 1963, 140, 299-309.

Prothypendyl chlorhydrate, Dominal, a new psycholeptic drug, has been helpful during childbirth, when the mother was agitated or suffered from anxiety. It can be used by itself or together with an antispasmotic drug, such as Buscopan. The drug can be given intramuscularly or orally. The preferred dosage is 40 mg since it is well tolerated by mother and fetus and has no side effects.

(No address)

422 Roy, Paul B., Mercure, Justin, Lebel, eorge, & Bourque, Robert. Contribution a 'etude du "Librium" dans le traitement es alcooliques. (Contribution to the study f Librium in the treatment of alcoholics.) 'Union Med. du Canada, 1963, 92, 218-221.

clinical study has been done recently to ssess the effects of Librium (chlordiaze- oxide) in 50 hospitalized alcoholics. ncouraging results in 89.8 percent of the atients was obtained. Undesirable side ffects such as ataxia, pollakiuria and ven enuresis in a few cases, were noted. uch effects are transitory and disappear y decreasing the dosage. The authors bserved that Librium may have a potentiat- ng action on alcohol. They feel that such n interesting possible effect of the drug s worth further and special investigation. owever, the most interesting effects of ibrium seem to be concerned with its emarkable action on anxiety and tension hich are the basic emotional trends in lcoholics. No habituation was found with ibrium. Finally, they report a typical ase to illustrate the advantages of ibrium and its significant effectiveness n preventing "delirium tremens."

o address)

423 Kafkalidis, Athanassios. Application herapeutique de la diethylamide de l'acide -lysergique (Delyside ou L.S.D.-25) sur es psychoneuroses. (Therapeutic applica- ion of the diethylamide of D-lysergic cid (Delyside or L.S.D.-25) to psycho- euroses.) Annales Medico-psychologiques, 963, 121(2), 191-200.

f nine patients treated with LSD-25, our suffered from chronic psychotic ten- ion with psychosomatic symptoms, two had bsessions, two depressions with anxiety, nd one was a chronic alcoholic. Two atients diagnosed as chronic psychotic ension recovered completely, four were onsiderably improved, and three were ailures. The author recommends that ecause of occasional resistance to LSD-25 he dosage should be increased gradually until the desired result is achieved. In one case up to 900 mu g of the drug was given each time. The strongest therapeutic dose for man is 12 mu g per kg. Beginning doses should never exceed 50 mu g for males, 30 mu g for females, intramuscularly or orally.

(No address)

424 Poldinger, W. Die Besonderheiten des Klinischen Wirkungsbiteles von Vesitan. (Peculiarities of the clinical effective- ness of Vesitan.) Therapeutische Umshau, 1963, 20, 68-70.

Vesitan has less extrapyramidal side effects than pure phenothiazine derivatives with a piperazinyl-propyl side chain because of one of its components: chlorphencyclan. By changing the dosage, not only the quanti- tative but also the qualitative aspects can be changed. Thus, it will not only be beneficial as a psychopharmacological agent but also aid in the "remobilization" of chronic schizophrenics with autism. In patients with stupor intravenous administra- tion shows quick results. In some cases it can replace electroshock therapy.

Kantonalen Psychatreschen Klinik
St. Urban, Luzern, Switzerland

425 Drolet, Conrad, Johnson, Gerard, & ourque, J.-C. Emploi du Librium intra- veneux dans la cuie de desintoxication alcoolique. (The use of intravenous Librium in alcohol deintoxification treat- ments.) Laval Medical, 1963, 34, 313-315.

Intravenous Librium has been successful in the control of anxiety in alcoholics. The action is almost immediate as excita- tion stops and the patient falls into peace- ful sleep. The authors suggest that this same effect may be obtained in patients with anxiety due to other factors than alcoholism. An added advantage to i.v. Librium is that it has almost no side effects. An accumulation of sedatives, given to alcoholics to control their

anxieties, has in some cases caused cardio-respiratory complications, which many times retard the success of the cure. This medication seems to simplify these difficulties.

(No address)

426 Rosen, A. Medikamento's bedingter Parkinsonismus und seine Behandlung mit Akineton. (Drug-induced parkinsonism and its treatment with Akineton.) Therapeutische Umshau, 1963, 20, 9-12.

Akineton (3-piperidino-1-phenol-1-bicyclo-heptenyl-propanol) is effective in cases of parkinsonism, caused by drugs. Twenty-three patients with this type of parkinsonism and nine patients with parkinsonism of other origin were benefited by the drug. In acute cases of dyskinesia, Akineton was extremely effective. In cases of tremor and allergic reactions, the drug was given in combination with Soventol. No side effects were noted even when the Akineton was given over an extended period.

(No address)

427 Freilinger, G. Schmerzbekämpfung bein gekreuzten Bruckenlappen. (Pain prevention in cross-bridged flaps.) Chirurg, 1963, 34, 108-111.

Niamid has been successfully used on patients whose joints had to be immobilized in preparation of skin grafts. The intense pain caused by immobilization was avoided by pretreating the patients with Niamid. The optimum dosage was 25 mg, 2-4 times daily. Three case reports are given.

Chirurgeschen Universitatsklinik
Wien, Austria

428 Vallade, Boutillier, Corsetti, Raybaud, & Ducamin. Premiers resultats de pratique du 8089 C.B. en therapeutique psychiatrique apropos de quatre observation. (First results of the use of 8089 C. B. in psychiatric therapy, apropos of four cases.) Annales Medico-Psychologiques 1963, 121(1), 233-239.

Benzoperidol, 8089 C.B., a butyrophenon, was given to a group of 25 women diagnosed as psychomotor agitation (15), behavioral or character disorders (8), and pithiatism (2). Of the 15 patients with psychomotor agitation, 66 percent had favorable result of the 8 with character or behavioral disorders, 7 had good results, 1 fairly good results. The two other patients were failures. Dosages were 4 mg parenterally, and 16 mg orally, as a maximum. Treatment usually lasted from 3 weeks to 1 month. Side effects included drowsiness, insignificant elevation of blood pressure, and muscle spasms. The effects of the drug on the EEG seemed very moderate. Since all results are based on a small number of patients, the authors feel that a final conclusion cannot be drawn, but that they consider it a worthwhile psychopharmacological drug which is well tolerated and has insignificant side effects.

(No address)

429 Borenstein, P., Bles, G., Croize, B. & Vansteenbrugghe, A. Le Valium: etude clinique et electroencephalographiqu Resultats et indications. (Valium: a clinical and encephalographic study. Results and indications.) Annales Medico-Psychologiques, 1963, 120(2), 604-612.

Valium, like Librium, is a benzodiazepine, with similar pharmacological effects. It was given to 140 patients whose diagnoses were schizophrenia (30), chronic delirium (24), symptoms of confusion (11), outburst of raving (15), mania (10), and depression (50). Of this group, 84 were greatly or slightly improved; the symptoms were aggravated in 20 patients and 36 were unchanged. Administration of the drug was

either parenteral or oral. Maximum dosage was 60 mg i.m. or 80 mg orally. The average dosage varied from 20 to 40 mg and from 30 to 60 mg. In 45 cases, additional medication in the form of amitriptyline, haloperidol, and chlorpromazine was given. Side effects were debility and tiredness, drowsiness, disturbances of the autonomic nervous system, hypotension, tremor. Electroencephalographic changes are described.

(No address)

430 Steinhoff, Horst E. Operationsvorbereitung mit Emesis-Prophylaxe. (Preparation for surgery by emesis prophylaxis.) Deutsches Medizinisches Journal, 1963, 14, 47-48.

A group of 246 patients was given 20 mg Psyquil, a phenothiazine derivative with 1 ccm dilaudid-atropine-weak (W. Z. Knoll), i.m. 2 hours before surgery. The patient became relaxed and quiet so that operations could be performed under local anesthesia. Lowering of the blood pressure was insignificant. Postoperative vomiting was greatly reduced by Psyquil.

(No address)

431 Wickstrom, Jack, & Haddad, Ray. An evaluation of the muscle relaxant properties of Librium. Journal of the Louisiana State Medical Society, 1963, 115, 140-145.

A group of 70 patients with painful spastic disorders, bone fractures, and musculoskeletal trauma was given Librium to determine its muscle relaxant potential. Ninety-five percent obtained relief as opposed to 48 percent of the placebo group, in this double-blind study. Side effects were noted in the drug as well as the placebo group. These consisted of drowsiness (8), dizziness (2), and increased libido (1). Slight reduction in dosage reduced the severity of the side effects.

New Orleans, Louisiana

432 Peck, Robert E. A validation of Hoffer's atropine test. Diseases of the Nervous System, 1963, 24, 84-89.

Hoffer's atropine test has been found useful in determining if patients are truly schizophrenic or nonschizophrenic. The cases selected for the study were either acute or chronic cases of schizophrenia; the nonschizophrenics were patients with various types of depression, alcoholics, and sociopaths. They were given two injections, one saline control injection and one atropine injection, while their blood pressure was being taken. Efforts were made to control experimental and diagnostic errors. The schizophrenics' pressure remained the same or fell after atropine injection; the nonschizophrenics' blood pressure rose. There were few side effects. Most subjects complained of dry mouth and dizziness.

Meadowbrook Hospital
East Meadow, New York

433 Ravetz, Elkin. Choral betaine in the management of mentally disturbed senile patients. Current Therapeutic Research, 1963, 5, 75-80.

Choral betaine (Beta Chlor) has been successfully used in elderly patients, most of whom were suffering from chronic brain syndrome. It induces sleep without depressive aftermath or gastrointestinal disturbances. In mildly agitated patients with confusion and disorientation it had a significantly sedative action. The action of the drug is easily controlled by graduating the dosage. Chloral hydrate is rapidly metabolized. Its most important metabolite, trichloroethanol, is primarily responsible for its hypnotic effect. The drug is administered per os in tablets of 870 mg (500 mg of chloral hydrate) and 435 mg (250 mg of chloral hydrate). Of the 27 patients (22 female and 5 male) with an average age of 72 years, 18 experienced a satisfactory night's sleep of 6-8 hours.

West Haven Nursing Home
Broomall, Pennsylvania

434 Dolmierski, R., & Smoczynski, S. Studies on the therapeutic value of atropine coma. Bulletin of Polish Medical Science and History, 1963, 6, 64-67.

Thirty-five psychotic patients who were unresponsive to other treatment methods were treated by means of atropine coma. Before and after treatment, blood, urine and cerebrospinal fluid examinations, EEG, EKG, PEG and chest x-rays were carried out. Five percent solution of atropine sulfate was injected. Physostigmine was used to discontinue the atropine coma. Patients also received 50 mg of chlorpromazine intramuscularly. Thirty to a hundred mg of atropine was injected. In most patients, difficulties in speech and concentration appeared in 5 minutes and after 10 minutes symptoms of somnolence appeared. Physiological measures were made throughout the treatment period. After 3-4 hours of coma, physostigmine was administered subcutaneously. Considerable improvement was obtained in patients with obsessional ideas and compulsory movements. Four cases are presented.

Department of Psychic Disorders
Medical School
Gdansk, Poland

435 Janecek, James, Schiele, Burtrum, & Vestre, Norris D. Pargyline and tranylcypromine in the treatment of hospitalized depressed patients. Journal of New Drugs, 1953, 3, 309-316.

Forty hospitalized depressed patients were randomly assigned to treatment with either pargyline (25 mg) or tranylcypromine (10 mg). The drugs were given orally on a double-blind basis for a 3-week period. Changes were evaluated by 1) judgment of global improvement, 2) the Brief Psychiatric Rating Scale, 3) the Clyde Mood Scale, and 4) the MMPI. The number of side effects for tranylcypromine was 58 and for pargyline 44. The authors concluded that tranylcypromine was superior to pargyline in the dosage levels used.

(No address)

436 Caffey, Eugene M., Jr., Forrest, Irene S., Frank, Thomas V., & Kleet, C. James. Phenothiazine excretion in chronic schizophrenics. American Journal of Psychiatry, 1963, 120, 578-582.

A study of the effects of discontinuing or reducing maintenance medication of 279 chronic schizophrenic males provided an opportunity to evaluate the clinical usefulness of a rapid semiquantitation urine test (FPN). Patients were randomly assigned 1 of 4 groups. One group continued to receive chlorpromazine or thioridizine daily at the established dose; a second group received a reduced dosage on an intermittent schedule; and a corresponding control group for each of the drug groups was given placebos. Patients in the first group continued to excrete at a regular rate and generally high level. The reduced intermittent group showed an initial decline but the curve flattened out at an intermediate level. The placebo group showed a rapid decline. The average baseline readings on the FPN test at different dosage levels were uniformly low for thioridazine.

Veterans Hospital
Perry Point, Maryland

437 Bennett, Jesse L., & Hamilton, L. Dean Sequential use of antidepressant drugs with chlorpromazine in chronic schizophrenia. Psychiatric Quarterly, 1963, 37, 53-66.

Each of 20 chronic schizophrenic male patients was treated with oral doses of dextroamphetamine (60 mg), imipramine (225 mg), isocarboxazid (30 mg), trifluoperazine (30 mg), or a placebo in combination with chlorpromazine (200-400 mg per day) for 5 months. There were 4 treatment groups and 1 placebo control group. A double-blind technique with random assignment was used. Two additional control groups were maintained on 200 to 400 mg of chlorpromazine. Clinical changes were measured by the Inpatient Multidimensional Psychiatric Scale, the Psychotic Reaction Profile, and a Composite Clinical Evaluation. At the end of the first 3-month

eriod, 3 patients showed improvement; owever, at the end of the second sequential eriod of 4 months, 3 patients were in emission, 3 were much improved, 2 were mproved, 6 were slightly improved and 6 howed no change. At the end of 1 year of reatment, 6 were in remission, 4 much mproved, 5 improved, 4 slightly improved, nd 1 patient showed no improvement. A ollowup of patients 1 year following ermination of treatment showed 17 patients ischarged from the hospital, 1 released nd returned, and 2 patients remaining in he hospital. The sequence of antidepressant rug administration did not show any pattern hen correlated with clinical improvements. ontrollable complications of hypotension, arkinsonism, and akathisia occurred.

eterans Administration Hospital
alt Lake City, Utah

438 Bartholomew, Allen A. An assessment of the therapeutic efficacy of "Trepidone." Medical Journal of Australia, 1963, 50, 150-151.

A double-blind study was made to evaluate Trepidone (a methyloxyphenoxymethyl derivative of oxazolidonone) in 24 neurotics and 40 alcoholics. All patients were given a placebo the first week; nothing the second week. The third and fourth weeks of the study the experimental group was given 1,600 mg of Trepidone per day and the control group a placebo. Supportive psychotherapy was given throughout. In the neurotic experimental group, 5 out of 12 were improved; in the alcoholic group, 9 of 20 in both the experimental and placebo groups were improved. Side effects included anxiety, nausea, headache, and sleep disorders.

Alexandria Clinic
Department of Mental Hygiene
Victoria, Australia

439 Scott, J. C. Phenistix in psychiatric practice. Scottish Medical Journal, 1963, 8, 30-33.

Morning urine specimens from 600 mental patients were subjected to the Phenistix test to detect whether or not chlorpromazine was being taken as directed. Positive reactions resulted in 88 percent of the men and 87 percent of the women. In view of this high detection ratio, urine specimens were obtained from 100 male patients; 62 of whom were receiving chlorpromazine (average dose of 236 mg/day) and 38 who received no drugs, and 53 of the 62 patients on chlorpromazine yielded positive Phenistix tests. In an effort to make accurate drug detections, 8 patients received chlorpromazine for 3 months, after which therapy was abruptly discontinued. Phenistix results were positive in 4 patients, 56 hours after drug withdrawal, but negative in all patients after 62 hours. A single oral dose of chlorpromazine (50-100 mg) administered to 9 patients who were drug free for 3 months, yielded positive Phenistix results at 2 hours, in 6 patients at 6 hours, and in no patients at 10 hours. Survey of the hospital population yielded 62 positive reactions which were not due to chlorpromazine metabolites.

Royal Mental Hospital
Dundee, Scotland

440 Moriarty, A. J., & Nance, M. R. Trifluoperazine and pregnancy. Canadian Medical Association Journal, 1963, 8, 375-376. (Letter)

A study of the incidence of congenital malformations in offspring of women who had received trifluoperazine during pregnancy compared with women who had not revealed any evidence of a causal relation between the administration of the drug and the production of congenital malformations. To determine if evidence of a causal relation existed, 472 cases in the trifluoperazine files of a drug company were reexamined. Cases representing a baseline incidence of congenital malformation were drawn from a source as similar as possible to the source of the trifluoperazine cases and which antedated the introduction of both thalidomide and trifluoperazine. Incidence data and conditions of abnormality are presented for both groups.

Smith, Kline, and French Inter-American Corporation
Montreal, Canada

441 Braun, Manfred. Phenothiazines and cardiac arrest after ECT. American Journal of Psychiatry, 1963, 119, 796.

It is suggested that phenothiazines and reserpine be discontinued at least 1 week prior to administration of ECT. The author contends that a single dose of phenothiazines can be found in a patient's urine many days after the medication was administered. The autonomic nervous system effects of 25 mg levomepromazine given to a 62-year-old patient were possibly potentiated by 250 mg Evipan-Natrium i.v. and complicated by the stress of ECT the following morning, when the patient experienced cardiac arrest.

V.A. Hospital (NP Service)
Bronx 68, N.Y.

442 Nystroem, Sune. Reply to the foregoing. (Phenothiazines and cardiac arrest after ECT.) American Journal of Psychiatry, 1963, 119, 796-797

In relation to Braun's (1963) warning that phenothiazines should be discontinued 2-4 days before ECT, the following is stated. Although no definitive correlation has been established between cardiac arrest after ECT combined with phenothiazines, previous work has indicated that all four patients who had been treated with phenothiazines before ECT-death died of cardiac failure. Chlorpromazine in combination with ECT is known to cause marked hypotension. In five cases of ECT-death where patients had not received phenothiazines, two died in cardiac failure and three from unrelated diseases. It is quite possible phenothiazine pretreatment may lead to collapse.

Psykiatriska Kliniken
Sahlgrenska Sjukhuset
Goteborg SV, Sweden

443 Dilworth, N. M., Dugdale, A. E., & Hilton, H. B. Acute poisoning with chlorpromazine. Lancet, 1963, 7273, 137-138.

The effect of an acute overdose of the widely used tranquilizing agent, chlorpromazine, is often lethal with primary involvement of the cardiovascular and neuropulmonary systems. A case report involving a healthy $3\frac{1}{2}$-year-old white male who ingested 800 mgm of chlorpromazine is described. The principal clinical features noted before the patient's demise within 3 days involved basic cardiovascular and neurorespiratory mechanisms. Respiratory depression, hypotension, and gradual loss of consciousness were the primary problems to be dealt with. Analeptics such as nalorphine, picrotoxin, bemegride, and amiphenazole were of limited value in offsetting the progression of the cardiopulmonary collapse. The most useful vasoconstrictors applied to maintain the blood pressure were phenylephrine and noradrenaline. Intravenous therapy was found

to be necessary because of the patient's state of consciousness as well as the presence of a paralytic ileus. The fluid usually composed of varying mixtures of dextrose and water supplemented by minerals (potassium and chloride) and vitamins should be sufficient to offset the diuresis which occurs secondary to depression of hypothalamic mechanisms involving the production of the antidiuretic hormone. Exchange transfusion is not recommended since the chlorpromazine is fixed in the tissues by the time there are signs and symptoms of a severe overdose. Pathologic findings stress the toxicity of the drug to liver parenchymal tissue and cerebral vascular tissue.

Princess Margaret Hospital For Children
Perth, Western Australia

444 Sours, John A. Acute intestinal obstruction with volvulus in akinetic mutism. Journal of Neuropsychiatry, 1963, 4, 232-235.

Because of the difficulty in diagnosis as well as the high mortality risk it is important that a masked intestinal obstruction be considered when an akinetic mutistic patient develops abdominal signs or even an equivocal fever. There are many difficulties in diagnosis and treatment presented by the mute hypokinetic or a kinetic patient who can mask the signs and symptoms of intestinal obstruction. In order to illustrate this impression, a case report of a 47-year-old married woman, who describes an episode of brief unconsciousness associated with subsequent mutism and negativism for several hours, is discussed. The patient underwent many diagnostic studies including x-rays, lumbar punctures, electroencephalogram, neurological examination, special blood studies and finally an exploratory laparatomy which confirmed a volvulus and perforation in the small intestine. This patient clearly illustrated the differential diagnostic problems the akinetic presents with an intestinal obstruction, a problem which is becoming more frequent due to the widespread use of neuroleptic drugs particularly the phenothiazines which are generally thought to decrease intestinal motility and at times bring about constipation and intestinal obstruction.

U. S. Naval School of Aviation Medicine
Pensacola, Florida

445 Spencer, G. T., & Smith, S. E. Dangers of monoamine oxidase inhibitors. British Medical Journal, 1963, 5332, 750. (Letter)

Phenelzine (Nardil) is suggested as responsible for later abnormal responses to papaveretum. A case report is presented of a patient (weighing 74 kg) to whom papaveretum 10 mg and L-hyoscine 0.4 mg were given as premedication for a bilateral myringotomy. Previous treatment included phenelzine, 15 mg t.d.s., chlordiazepoxide (Librium), 10 mg t.d.s., and Gower's mixture. Abnormal symptoms noted after premedication included unrousability, peripheral dilation, and sweating. Gelsemium in Gower's mixture is considered of possible concern but phenelzine is considered as the responsible agent. (1 Ref.)

Department of Anaesthetics
St. Thomas's Hospital
London S.E.1, England

446 Twyman, James B. Acute extrapyramidal reaction associated with trifluoperazine. Virginia Medical Monthly, 1963, 90, 132-133.

A 25-year-old woman with severe headaches received dextropropoxyphene (1 capsule q.i.d.) and trifluoperazine (2 mg b.i.d.) for 2 days, after which she suddenly experienced dyspnea, dysphagia, dysarthria, paroxysmal pain involving difficulty in swallowing. Mepergan (methidene and promethazine, 1 cc i.m.), Diphenhydramine (50 mg), phenobarbital (16 mg), and diphenylhydantoin (100 mg) alleviated muscular hypertonicity and trismus and all neurological aberrations subsided within 4 days. The trifluoperazine intoxication observed was severe enough to simulate tetanus.

400 Locust Avenue
Charlottesville, Virginia

447 Watson, G. I. "Ancoloxin" and foetal abnormalities. British Medical Journal, 1963, 5323, 122. (Letter)

The newly instituted Register of Unexpected Toxicity incorporated a list of drugs from the Journal of the College of General Practitioners which encompassed all compounds subject to sufficient suspicion to indicate the need for further experimental inquiry. Listed drugs utilized in pregnancy included perphenazine, pipamazine, prochlorperazine, promethazine, Ancoloxin (meclozine and pyridoxine) and chlorpromazine, each of which was administered during a pregnancy which ended in congenital abnormality. Other reports implicated thalidomide, glutethimide, buclizine, and Debendox (dicyclomine, doxylamine, and pyridoxine). Numerous reports of deleterious effects from the above drugs have been accumulated recently. Final judgment will be suspended until considerably more information has been assimilated and exhaustively analyzed. Specialists have been assigned the task of determining the absence or presence of teratogenicity and the relationship between illness, drugs, and other circumstances which might adversely affect pregnancy. Statistical analyses are being performed on data derived from all available information of fetal malformations. Statistics confirm that meclozine is harmless to the majority of babies when administered during pregnancy. It is essential that the antiemetics administered during the early months of pregnancy be absolutely safe.

Epidemic Observation Unit
College of General Practitioners
Guildford, Surrey, Great Britain

448 Whittaker, C. B., & Hoy, R. M. Withdrawal of perphenazine in chronic schizophrenia. British Journal of Psychiatry, 1963, 109, 422-427.

In the course of 52 days, 10 major and 7 minor relapses were experienced with 26 schizophrenic patients when perphenazine was abruptly withdrawn. Subjects were 39 male chronic schizophrenics, all with a paranoid condition; 2 also had catatonic tendencies and another hebephrenic features. All had been receiving maintenance doses of perphenazine for an average of 16 months with no recent condition changes. The patients were arbitrarily allocated to 3 groups of 13; one group received perphenazine in the usual dose, a second group received a placebo, and the third received no perphenazine. The trial was blind with respect to the latter two groups. A major relapse was counted if a patient had to be replaced on a preparation known to be active. Minor relapses were determined on the basis of nurses' ratings on a behavior rating scale. The results of a third criterion measure, a psychiatric rating scale, are not dealt with in the report. Implications regarding the feasibility of discontinuous perphenazine treatment are drawn.

Gartloch Hospital
Glasgow, Scotland

449 Dembicki, Eugene L. Psychiatric drugs and trends. Journal of Psychiatric Nursing, 1963, 1, 21-22.

Tranylcypromine and amitriptyline are recommended as drugs for depression. Side effects, precautions, and dosages are discussed. The major side effects of tranylcypromine appear to be restlessness, overstimulation, and insomnia. It is contraindicated in patients with a history of liver disease or with abnormal findings in liver function tests. The side effects of amitriptyline are drowsiness, dizziness, nausea, excitement, hypotension, tremor, headache, heartburn, anorexia, perspiration, and skin rash. Caution is advised when a patient is transferred from MAO inhibitors to this drug because it may potentiate other antidepressants.

(No address)

450 Simpson, J. A., Evans, J. I., & Sanderson, I. D. Amblyopia due to phenipracine. British Medical Journal, 1963, 5326, 331.

The case of a 50-year-old male is described who suffered from an irreversible bilateral

ptic atrophy after being treated with
heniprazine for 30 months. The drug had
een prescribed for endogenous depressive
llness and the patient was given 9 mg per
iem. After 15 months of treatment, color
lindness set in and a small central visual
ield defect was detected along with the
erve atrophy. The drug was discontinued
hile no improvement of the condition took
lace; no further deterioration of vision
as noted either. In earlier reports by
ther authors, 6 out of 21 patients on the
ame drug had also developed red/green color
lindness.

eurological Unit
orthern General Hospital
dinburgh 5, Scotland

51 Womack, A. M. Sudden death during
reatment with tranylcypromine. British
edical Journal, 1963, 2, 366.

ranylcypromine, an antidepressant drug of
he MAO-inhibitor-type, is blamed for the
eath of a physically healthy grammar-
chool boy with depressive illness. This
rug, which is known to provoke acute hyper-
ensive reactions with severe headaches,
alpitation, vomiting, and collapse, was
iven to the patient in the form of
parstelin" (10 mg tranylcypromine and
mg trifluoperazine per tablet). He
eceived 1 tablet daily for 2 weeks then
ncreasing to 2 a day. On the 15th day,
e collapsed after an agonizing headache
nd pounding in the chest. Necropsy find-
ngs indicated acute circulatory failure.
t was assumed that death was caused by
rovoking a hypertensive crisis and
ardiac arrhythmia.

ury General Hospital
ngland

452 Pharmaceutical Journal. Habituation to amphetamine. Pharmaceutical Journal, 1963, 190, 22.

A survey shows that one in five women and one in four men taking amphetamine are liable to become habituated. Some 620 patients were given amphetamine or related drugs for a 3-month period. The average daily dose was equivalent to 10 mgm of dexamphetamine sulfate; 85.5% of the patients were women. In the opinion of the prescribing doctors, 20.5% of the patients were habituated. The tendency toward habituation was greatest in the over 65 age group. The anorexic effect of the drug failed after prolonged use.

(No address)

453 Schrire, I. Trifluoperazine and foetal abnormalities. Lancet, 1963, 7273, 174.

The author suggests that instances of skeletal and other abnormalities in newborn are merely coincidental to the treatment with trifluoperazine because of the very large number of patients treated with the drug and the small number of reported abnormalities. Of the eight cases with congenital deformities reported in Canada, five of the mothers had taken various other preparations before and after conception. In three patients, no details were available.

Smith, Kline, and French Laboratory
Welwyn Garden City, Hertfordshire, England

454 Council on Drugs--American Medical Association. Paradoxical hypertension from tranylcypromine sulfate. Journal of the American Medical Association, 1963, 186, 854.

Tranylcypromine sulfate, because of its severe side effects which have sometimes resulted in death, should not be given to patients with suspected cerebrovascular defect or with severe cardiovascular disease. Adverse effects reported include headaches, palpitation, nausea, vomiting, stiffness of neck, photophobia, tachycardia or bradycardia, and chest pain. The author recommends that therapy be discontinued when any of these symptoms occurs. Tranylcypromine should also be avoided in conjunction with amitriptyline, imipramine, or other MAO-inhibitors. It can produce a reduction in blood pressure when it is used concomitantly with meperidine and other narcotics, barbiturates, phenothiazine compounds, and the thiazide diuretics.

(No address)

455 Brachfeld, Jonas, Wirtshafter, Alan, & Wolfe, Sheldon. Imipramine-tranylcypromine incompatibility. Near-fatal toxic reaction. Journal of the American Medical Association, 1963, 186, 1172.

Serious side effects, including fatalities, have been reported with the combination of imipramine hydrochloride and MAO inhibitors. A case report is given where 1 tablet of imipramine given 3 days after the MAO inhibitor had been stopped produced a deeply comatose state. A 41-year-old female had received tranylcypromine, 10 mg t.i.d. for 3 weeks. Three days after cessation of this therapy she had taken 1 tablet of imipramine. Severe headaches, loss of consciousness, and convulsions followed. Temperature rose to 105° F. On admission to the hospital, 250 mg of amobarbital sodium and 100 mg of dophenylhydantoin sodium i.v. were administered. Additional doses of amobarbital were markedly beneficial and the patient recovered. It is suggested that depressed patients about to receive antidepressant medication should be questioned about previous medication within the preceding 2 weeks.

(No address)

456 Charalampous, K. D., & Hug, A. Psychosis following the use of amphetamines. Medical Record and Annals (Houston), 1963, 56, 31-32.

The authors describe the syndrome frequently encountered in psychiatric practice, one result of amphetamine abuse, which often passes undetected. Amphetamines are addictives and the clinical practice following the use or withdrawal from excessive amount is that of a paranoid psychotic reaction. The frequent absence of disorientation may distract one from recognizing the toxic state; the acuteness of the episode, however, may cause the physician to suspect it. The treatment for the psychotic phase is non-specific. Abrupt withdrawal from the drug, hospitalization, and some sedation are in order. Suicide may be a risk during the withdrawal phase. Treatment should be directed to curing the addiction and the antecedent emotional problems.

Baylor University College of Medicine
Houston, Texas

457 Merchant, H. C., Ramamoorthy, K., Choksi, N. D., & Shikaripurkar, N. K. A fatal case of acute chlorpromazine poisoning. Journal of the Association of Physicians of India, 1963, 11, 337-339.

A case report is given of a 19-year-old male who ingested 250 mg chlorpromazine for the relief of post-operative pain and who died 18½ hours after having taken the drug from acute poisoning. Chemical analysis of the stomach washings did not reveal presence of chlorpromazine. The quick metabolism of this drug has been previously described by other authors who found only small amounts in the plasma 3 hours after i.v. administration. In some cases up to 4,800 mg per diem have been given to patients and were well tolerated. The usual dose is 300-2,500 mg per diem.

L. T. M. G. Hospital
Sion Bombay 22, India

458 Cullen, W. The treatment of depression with tranylcypromine ("Parnate"). Journal of the Royal Naval Medical Service, 1963, 49, 37-43.

The author reviews various treatments for depression. The literature surveyed suggests that tranylcypromine (Parnate) is an effective method of treatment. Most workers have reported a 70% recovery rate. No cases of liver dysfunction or of blood dyscrasia were noted and no changes in pattern of cerebral activity during treatment were shown in EEG studies. Hypertension, headache and two cases of death by cerebral hemorrhage were reported. The two cases suggest that tranylcypromine must be used with skill and caution.

(No address)

459 Cranswick, E. H., & Simpson, G. M. Perphenazine and thyroid function. Journal of the American Medical Association, 1963, 186, 1102. (Letter)

The authors refute a criticism of their findings of raised protein-bound iodine (PBI) levels in mental patients receiving perphenazine medication. The authors compared a group of perphenazine treated patients with a group of patients who had never received perphenazine. The perphenazine group had a mean PBI of 9.0 mg% while one control group was 6.0 mg%. Reports of other investigations which indicate that perphenazine changes thyroid iodine are discussed.

(No address)

460 McConnell, W. B. Amphetamine substances in mental illnesses in Northern Ireland. British Journal of Psychiatry, 1963, 109, 218-224.

In a group of 20 women and 11 men referrals, amphetamine analogs played an important part in the causation of their presenting symptoms. Six patients had symptoms which were clinically indistinguishable from paranoid schizophrenia. All were tense, evasive, and suspicious with disordered mood and paranoid delusions. Auditory and visual hallucinations were present. In most of these patients improvement began to occur within a week after the drug had been discontinued. There was evidence that half of these patients returned to their addiction after discharge. A second group contained 20 patients who were addicted or habituated. Seven of these patients were "symptomatic addicts," since at different times they would be dependent on different drugs. Thirteen of the addicted patients were dependent of this drug alone. Five patients were seen in which the side effects of amphetamine were predominant as presenting symptoms. They were referred with anxiety, tension, restlessness, severe headache, and/or dizziness. Improvement was noted with discontinuation of the medication. The author presents a lengthy discussion of paranoid states and other undesirable effects of the amphetamines. He further suggests that a problem of amphetamine abuse exists in Northern Ireland.

Department of Mental Health
The Queen's University
Belfast, Ireland

461 Centre National de la Recherche Scientifique. Psychophysiologie, neuropharmacologie, et biochimie de la crise audiogene. (Psychophysiology, neuropharmacology, and biochemistry of the audiogenic seizure.) Paris: Centre National de la Recherche Scientifique, 1963. (Colloque Internationaux du Centre National de la Recherche Scientifique, No. 112. Gif-sur-Yvette, November 6-9, 1961.)

This book presents the proceedings of an international symposium on audiogenic crisis which was held in Gif-sur-Yvette in November, 1961. Studies include information on psychophysiological, physiological, biochemical, and neuropharmacological aspects of audiogenic seizures in animals. The studies are of significance because this condition in animals serves as a good experimental model from which to study human epilepsy. (580 Refs.)

(No address)

462 Costello, C. G. & Smith, C. M. The relationships between personality, sleep, and the effects of sedatives. British Journal of Psychiatry, 1963, 109, 568-571.

In order to compare the effects of sedatives on total sleep, 11 extraverts and 11 introverts (scored on Maudsley Personality Inventory at least 1 standard deviation above or below the mean of a group of 228 psychiatric patients) were matched on the basis of sedative and dose. Sleep records (nurses' judgments) of these patients who were not on medication during the day indicated no significant difference for extraverts between sedative nights and no sedative nights. Mean hours of sleep for the introverts on sedative vs. no sedative nights was significant ($p < .001$). Ten introverts and 10 extraverts on medication who were matched on this additional basis showed no significant differences for sedative and no sedative nights. Combining the groups not on medication with those who receive medication showed that 12 of the 21 extraverts slept less after sedatives while 5 of the 21 introverts slept less ($p < .05$). These results are seen as supporting the hypothesis that the sleep of introverts after administration of a sedative would improve to a greater extent than that of extraverts. This prediction was made by the authors on the basis of the theory of paradoxical excitation. A further prediction that extraverts would sleep longer than introverts was confirmed. Other hypotheses regarding the sleep of patients with anxiety reactions and reactive depressions were not confirmed.

Monroe Wing, Regina General Hospital
Regina, Saskatchewan, Canada

463 Caird, W. K., Laverty, S. G., & Inglis, J. Sedation and sleep thresholds in elderly patients with memory disorder. Gerontologia Clinica, 1963, 5, 55-62.

Memory-disordered patients showed statistically significant, <.01, lower sedation and sleep thresholds than matched controls. An experimental study in which 10 psychiatric patients diagnosed senile dementia were compared with 10 paranoid schizophrenic or depressive patients. All experimental subjects were clinically estimated as having undoubted memory disorder. Control subjects were without memory disorder. Groups were matched for age (all adults, 64 + years), body weight, WAIS IQ's, and paired-associate learning. Method for determining sedation threshold and sleep threshold was a simplification of that used by Claridge and Herrington (Journal of Mental Science, 106, 1960) to have subject add 1 to a list of random 2-digit numbers. Sodium amytal in solution of 0.5 grain per cubic centimeter of distilled water was injected at the rate of 0.5 grains per minute. Sedation threshold was calculated in terms of milligrams sodium amytal in relation to kilograms of body weight. Sleep threshold was calculated from the point at which subject no longer responded to verbal stimulation. The statistically significant, $p < .01$, lower thresholds of the memory-disordered subjects is seen as offering support to the hypothesis that lowered energy of CNS reverberatory oscillations that underlie the disability of short-term memory should show greater susceptibility to the effects of anesthetics. The technique employed is suggested as possibly useful in early detection of incipient memory disorder.

Department of Psychiatry, Queens University
Kingston, Ontario, Canada

464 Clark, Fogle C., & Steele, Bobby J. Some observations on the interaction of chlorpromazine and free operant avoidance bursts. Psychopharmacologia, 1963, 4, 221-231.

The removal of an idiosyncratic dose-response relationship through manipulation of an associated property of baseline avoidance behavior is demonstrated. Rate of avoidance responding under Sidman schedules is normally decreased by

ncreasing doses of chlorpromazine and is ccompanied by an increase in the shock ate. In a rat displaying a strong pattern f post-shock bursts of lever pressing, he usual effect of chlorpromazine dosage n shock rate was obtained, but the response ate was increased by intramuscular doses f less than 1 mg/kg. Through the addition f a schedule which punished responses in ursts, nearly all bursts of more than two esponses were eliminated. A second hlorpromazine series obtained with the dded punishment then yielded a typical ose-effect relation for both response and hock rates. The possibility that apparently idiosyncratic dose-response functions n behavioral pharmacology may be due to imilar drug-behavior interaction is discussed.

Evansville State Hospital,
Evansville, Indiana

465 Lauener, H. Conditioned suppression in rats and the effect of pharmacological agents thereon. Psychopharmacologia, 1963, 4, 311-325.

Male albino rats received various CNS-active drugs to test for action on conditioned suppression or conditioned emotional response (CER). The conditioning signal was followed by an unavoidable electric shock. Of the 17 drugs tested, 9 inhibited and finally abolished the CER. Eight drugs were inactive. Thirty rats of the Wistar strain were rewarded water on pressing a lever at intervals of 5 seconds. A variable relatively short duration of signals was chosen. A regular schedule of relatively frequent rewards was given because this increases the number of lever-presses (LP) which is advantageous in statistical evaluation. The sequence of treated and untreated rats was randomized. The test drug dosage was determined in such a manner that the highest dose was just below that which produces ataxia or diminished muscle tone. The highest dose used was that which produced no neurological disturbances. The decrease in lever-pressing activity during signals was very pronounced in untreated animals. Chlordiazepoxide inhibited the decrease in the CER rate during signals; it abolished the CER completely after oral administration of 20 mg/kg. Its effect had disappeared 24 hours after treatment. Other CNS active drugs such as phenobarbital, barbital, aprobarbital, methylphenobarbital, amobarbital, and chloral hydrate showed a similar effect, while meprobamate and carisoprodol were less effective. Chlorpromazine, hexobarbital, ethanol, cyclobarbital, methylpentinol, mephenoxalone, amphetamine, and morphine were inactive. The decrease in lever-pressing activity during signals was very pronounced in the untreated animals.

Research Institute of Dr. A. Wander, S.A.,
Berne, Switzerland

466 Cooper, R. M., & Krass, M. Strychnine: duration of the effects on maze-learning. Psychopharmacologia, 1963, 4, 472-475.

Strychnine sulfate was injected into 32 female rats 24 hours and 3 days, respectively, prior to maze learning. Their performance improved. It is assumed that either the drug or some effect of the drug on the body is relatively enduring for a long period. The study was carried out to determine if strychnine has an effect on maze performance several hours or days after injection. The rats used were 90 days old and weighed approximately 200 g. The mirror image of the second problem of the Hebb-Williams maze test was used. The animals were divided into three groups according to adaptation proficiency and assigned in a semirandomized fashion to four groups. The 2 experimental groups received 1.25 mg/kg of strychnine sulfate in water intraperitoneally 24 hours and 72 hours, respectively, before maze testing. Control animals received only the needle. The 72-hour groups (control and experimental) were tested 7 days after the 24-hour

groups. They were given 20 trials on the H-W maze problem. Both experimental groups made fewer errors than the controls even when the single strychnine injection was given 3 days prior to the test. These results suggest that a possible accumulative or sensitizing effect is indicated; while the opinion that strychnine is rapidly destroyed may be correct, it is possible that its effect on the nervous system or other systems is more lasting. It also has been found that male and female rats have different tolerances for strychnine, picrotoxin, and probably other stimulants. The lethal dose of strychnine for females is about 60 percent of that for males.

Department of Psychology, University of Manitoba, Winnipeg, Canada

467 Miller, A. I., D'Agostino, A., & Minsky, R. Effects of combined chlordiazepoxide and alcohol in man. Quarterly Journal of Studies on Alcohol, 1963, 24, 9-13.

Inconclusive findings were revealed in a study designed to test whether chlordiazepoxide in the usual clinical dosage in combination with alcohol causes behavioral patterns different from those seen with alcohol alone. Eight volunteer normal subjects of above average intelligence without acute or chronic physical or emotional illness each received 10 mg of chlordiazepoxide (Librium) or a placebo 4 times daily for 4 days in a crossover study. Therefore each subject was tested twice after drug and twice after placebo. On the fourth day of each test, 4 ounces of 94-proof whiskey was consumed in a fasting state and the effects on performance changes in social, physical, and psychomotor behavior were studied. The data showed no qualitative difference between the effect of chlordiazepoxide and placebo in social behavior or in physiological measurements (blood pressure, pulse, temperature) or in performance or intelligence tests produced by alcohol consumption in the experimental subjects. It is believed that more valid information might be obtained by using a better sample of the general population and by taking account of more comprehensive psychosociobiological factors.

Department of Psychiatry, Georgetown University Hospital, Washington 7, D.C.

468 Ekman, Gösta, Frankenhaeuser, Marianne, Golberg, Leonard, Bjerver, Kjell, Järpe, Gundla, & Myrsten, Anna-Lisa. Effects of alcohol intake on subjective and objective variables over a five-hour period. Psychopharmacologia, 1963, 4, 28-38.

The general impression that subjective variables might be more affected by alcohol than objective test performance was substantiated by this investigation whereby the general purpose was to study various effects of alcohol as a function of time measured from the moment of alcohol intake. Eight male subjects were studied during a 5-hour period following a single dose of 0.55 g of alcohol per kilogram body weight. The main variables of the experiment were a) blood-alcohol concentration, b) self-estimated degree of intoxication, and c) observed degree of intoxication. The subjective scales were obtained by the method of magnitude estimation. The two curves representing self-estimated and observed degree of intoxication were in very close agreement; in a general way they also followed the blood alcohol concentratio curve. In addition, self-estimates of certain mood variables were obtained and two objective performance tests were administered. Nearly all curves obtained in the experiment showed a peak at about 30-40 minutes after alcohol intake. The subjectiv variables appeared more affected by alcohol than the performance variables.

Psychological Laboratory, University of Stockholm, Stockholm, Sweden

469 Franks, Cyril M. The apparent failure of etnyl alcohol to inhibit the formation of conditioned eyeblink responses in man. Psychopharmacologia, 1963, 4, 433-440.

In a double-blind study with 60 normal male volunteers, it was found that there were no differences between the conditioned eye-blink response behavior of placebo and alcohol treatment groups. The 60 paid volunteers ranging in age from 21-48 years were divided into 2 groups. One received the active treatment consisting of a relatively large dose of alcohol (1 ml 90-proof blended whiskey). The placebo treatment consisted of an inconsequential dose of alcohol. Blood alcohol levels were assessed. After 90 minutes, an eye-blink conditioning procedure was carried out. The present experiment failed to inhibit eye-blink conditioning. The difference between earlier studies and this one is that no "no-treatment" group was included while in the former study the subjects knew neither the nature nor the properties of the concomitant treatments and placebo; they had no preconceived notions common to treatment and placebo alike. In this study, however, the subjects knew they were to receive alcohol, thus some conditioning effects could have been induced by suggestions and preconceived beliefs. If this hypothesis is correct, then the prediction could be made that the reduced response level should in quality and quantity produce conditioning curves similar to the impaired performances of extraverts, hysterics, psychopaths, and brain-damaged individuals receiving depressant drugs.

New Jersey Neuro-psychiatric Institute,
Princeton, N. J.

470 Appel, James B. Drugs, shock intensity, and the CER. Psychopharmacologia, 1963, 4, 148-153.

In this experiment the effects of a chronic dosage regimen of chlorpromazine and of reserpine on the conditioned emotional response (CER) were compared and evaluated and the interaction of shock intensity and drug effects was studied. With the use of a conditioning paradigm, variable interval (VI) rates and suppression ratios were used as measures of the effects of small doses of reserpine (0.2 mg/kg) and of chlorpromazine (1.5 mg/kg) in albino rats. It was found that reserpine reliably reduced the CER at a relatively low shock intensity (0.8 ma); with more severe shock (1.0 ma) the results were equivocal. Chlorpromazine inhibited the CER at 1.0 ma. At the dosage and time parameters studied, chlorpromazine induced less depression of VI rate than did reserpine. Recovery from reserpine effect was generally more gradual than recovery from chronic chlorpromazine treatment.

Yale University School of Medicine,
New Haven, Conn.

471 Petrinovich, Lewis. Facilitation of successive discrimination learning by strychnine sulfate. Psychopharmacologia, 1963, 4, 103-113.

An experiment is reported in which the effects of strychnine on a nonspatial learning problem were determined and in which strychnine side effects were assessed. Two strains of rats, Tyron maze brights and Tyron maze dulls, were run on a visual successive discrimination problem under three conditions: strychnine sulfate 1.0 mg/kg intraperitoneally (E); saline controls (C); and non-injected controls (N). For both strains, the E group learned the problem significantly faster than did the C and N groups, which did not differ from one another. An evaluation of emotional indices (defecation and running times) considered as side effects led to the conclusion that enhanced learning could not be explained as a result of side effects. In this connection, evidence is presented that the strychnine groups were significantly better learners in spite of disturbing side effects. The problem of placebo and untreated controls is discussed.

San Francisco State College
San Francisco 27, Calif.

472 Plotnikoff, N. A neuropharmacological study of escape from audiogenic seizures. In Centre National de la Recherche Scientifique. Psychophysiologie, neuropharmacologie et biochimie de la crise audiogene. (Psychophysiology, neuropharmacology, and biochemistry of the audiogenic seizure.) Paris: Centre National de la Recherche Scientifique, 1963.

The facility for escape and the effects of drugs on the responses of groups of mice susceptible to audiogenic seizures was investigated. The ataractics are effective antagonists of the fright response, whereas the sedatives were found to inhibit convulsions but not the preconvulsive phase of running. Significant differences in the degree of protection exerted by chlorpromazine and meprobamate could be demonstrated between DBA and Swiss strains. It was proposed that differential inbreeding of susceptible mice may provide a tool for studies on drug mechanism. It was demonstrated that an escape outlet resulted in marked reduction of convulsion in two strains of mice. The escape response was differently inhibited by chlorpromazine and phenobarbital.

Stanford Research Institute,
Menlo Park, Stanford, California

473 Klee, Gerald D. Lysergic acid diethylamide (LSD-25) and ego functions. Archives of General Psychiatry, 1963, 8, 461-474.

Lysergic acid diethylamide (LSD-25) is demonstrated to significantly affect ego functions falling within three realms: perception, thought, and motility. The purpose of this paper is to discuss the effects of LSD on perception, thought, and motility, the areas in which ego functions are considered to be involved. For this purpose, several hundred normal volunteer subjects received LSD with the dose used in psychological studies reported as ranging from 1 μg to 2 μg/kg body weight, orally administered. Basic psychological functior are affected proportionately with the dose administered. Profound alterations in spatial orientation are described by LSD subjects with the most striking being changes in visual and somesthetic perception. Human figure drawings done by many of the subjects gave evidence of the profound disorganization of body image experienced under LSD as well as revealing the state of defensive functioning and psychopathology, such as paranoid tendencie and confused psychosexual identification. Intellectual ability including memory and problem solving were impaired by LSD, proportionate to the dose. Definite impair ment of memory was demonstrated by use of the Wechsler Memory Scale on 16 subjects receiving a moderate dose of 72 μg LSD. The capacity for good judgment and impulse control was also impaired in a study employing the Porteus Maze Test which examines the subjects' ability to both inhibit impulsive solutions and execute critical planning toward the achievement of goals. (34 Refs.)

Psychiatric Institute, University of Maryland School of Medicine, Baltimore, Md.

474 Seiden, Lewis S., & Carlsson, Arvid. Temporary and partial antagonism by L-DOPA of reserpine-induced suppression of a conditioned avoidance response. Psychopharmacologia, 1963, 4, 418-423.

This study shows that the reserpine-induced suppression of the conditioned avoidance response (CAR) can be partially and temporarily reversed by L-DOPA administered subsequently to reserpine. Female white mice (10) and male hooded rats (10) were trained to avoid shock in a modified shuttl box. Following training, the animals were treated with 2.5 mg/kg reserpine (i.p.). The reserpine-treated mice showed virtually complete suppression of the CAR and 50 percent of the animals failed to make escape

response. L-DOPA (L 3,4-dihydroxyphenylalanine), the metabolic percursor of dopamine, noradrenaline, and adrenaline increased the number of avoidance responses. Three hours after the L-DOPA injection the effect no longer persisted. Side effects of L-DOPA treated mice were piloerection and moderate exophthalmus. Besides the suppression of CAR, locomotor activity was completely antagonized for approximately the same duration. Tests with rats showed very similar results. D-DOPA had none of the effects mentioned. (16 Refs.)

Department of Pharmacology, University of Goteborg, Goteborg, Sweden

475 Hearst, Eliot, & Whalen, Richard E. Facilitating effects of d-amphetamine on discriminated-avoidance performance. Journal of Comparative and Physiological Psychology, 1963, 56, 124-128.

Effects of elimination of escape opportunity and pretreatment with 3 mg/kg d-amphetamine were separately examined in male Osborne-Mendel rats which exhibited relatively poor performance in a discriminated avoidance-escape situation. Removal of escape opportunity led to a marked deterioration in avoidance performance which could be reversed by reinstatement of the escape contingency. D-amphetamine administration brought about a significant improvement in avoidance performance without affecting lever responding in non-CS periods. The drug also failed to affect responses to exteroceptive stimuli which had not previously been correlated with shock. The most logical explanation for d-amphetamine's effects is the drug-induced breakup of CS-induced freezing patterns.

Clinical Neuropharmacology Research Center, NIMH, Saint Elizabeth's Hospital, Washington, D. C.

476 Helper, Malcolm, M., Wilcott, R.C., & Garfield, Sol L. Effects of chlorpromazine on learning and related processes in emotionally disturbed children. Journal of Consulting Psychology, 1963, 27, 1-9.

The purpose of this study was to determine whether chlorpromazine changes the ability of emotionally disturbed children to learn and retain new associations. It is tentatively concluded that chlorpromazine impairs the attention span. It results also in a decrement of correct responses. The subjects were 39 children (19 drug subjects, 20 placebo) of an average age of 115 months. They were diagnosed as 1) adjustment reaction to childhood; 2) psychoneurotic disorders; 3) schizophrenic reaction, childhood type; 4) personality train disturbance; 5) chronic brain syndrome with psychosis. During the 4-week drug period, chlorpromazine and placebo were assigned randomly in a double-blind design. Dosage level was determined initially by weight and age of the subject. It was increased or decreased as required by side effects such as drowsiness, decreased motor activity, and extrapyramidal involvement. Paired associate learning was less efficient under chlorpromazine, especially on later learning trials and among initially slower learning subjects. Serial learning and tapping rate showed less consistent trends. Porteus Maze Mental Age scores also declined under chlorpromazine, while Q scores improved. Remote or immediate memory was not affected by the drug.

Nebraska Psychiatric Institute, Omaha, Nebraska

477 Hartman, Alan M., & Hollister, Leo E. Effect of mescaline, lysergic acid diethylamide and psilocybin on color perception. Psychopharmacologia, 1963, 4, 441-451.

Psychotomimetics enhance stimuli which evoke subjective color phenomena or even those not usually associated with visual phenomena. On the other hand, the usual perception of color, as judged by hue discrimination, may actually be slightly decreased. Volunteer subjects were given three psychotomimetic drugs: mescaline, 5 mg/kg; LSD-25, 1 mcg/K, and psilocybin 150 mcg/K; 18 of the 20 subjects received all three. Color experience was tested by applying stimuli involving color perception,

stimuli eliciting subjective colors, and stimuli usually devoid of visual experience. Three forms of analysis of drug effects were made as follows: 1) before-after drug administration differences; 2) subjects by trial analysis of variance of the pre-drug administration measures; and 3) complex mixed analysis of variance (effects due to subjects, drugs and interaction). All measures of color perception were affected. Elicitation of subjective color from flicker was increased by all three drugs, but less by psilocybin than by the other two. Visual effects, both color and pattern, were significantly increased by LSD and mescaline. Spectral patterns of evoked colors varied slightly between the three drugs.

VAC, Gulfport Division, Biloxi, Mississippi

478 Ray, Oakley S. The effects of tranquilizers on positively and negatively motivated behavior in rats. Psychopharmacologia, 1963, 4, 326-342.

The results of this study show that appropriate doses of meprobamate, chlorpromazine, and reserpine act primarily on the negatively motivated behavior in rats and at these doses did not have a general effect on motor activity or stimulus input. This study was undertaken to determine whether the effect of tranquilizers in blocking the negatively motivated avoidance behavior was due to nonspecific effects on motor activity and/or stimulus input. In this procedure, these effects were differentiated by combining conditioned approach and conditioned avoidance trials in a single experimental session and by studying drug action when the animals were running under no shock, extinction conditions. The subjects were 40 male albino rats. After training in classical conditioned avoidance, the behavioral effects were studied following the interperitoneal administration of the three tranquilizers and one sedative (pentobarbital). The tranquilizers had their principal effect on the negatively motivated avoidance response, while pentobarbital did not show this sedative action. Instead it increased or blocked response latencies to both the food-paired stimulus and the shock-paired stimulus. (7 Refs.)

Veterans Administration Research Laboratories in Neuropsychiatry, Pittsburgh, Pa.

479 Rech, R. H., & Hale, M. E. Antagonism of reserpine behavioral depression by d-amphetamine. Federation Proceedings, 1963, 22, 568. (Abstract)

Amphetamine antagonized reserpine-inhibited locomotor activity in mice. Although the antagonism was poor 8 hours after reserpine at 24 hours amphetamine induced more activity than it caused in control animals. These studies, however, involved toxic dose of the drugs. With lower doses, we determined the time-response relationships of reserpine depression and of its antagonism by dexamphetamine on the conditioned avoidance responses of rats in a shuttle box. After the rats established a stable conditioned behavioral response (CBR), reserpine 1-2 mg/kg i.p., was found to depress CBR progressively with time. The nadir of depression (0%-75% of control) occurred in 8-24 hours; rapid recovery began 48-72 hours after reserpine. Dexamphetamine was a poor antagonist when injected i.p. 2.5 hours after reserpine. At 8, 12, and 24 hours post-reserpine, dexamphetamine was much more effective (best at 24 hours). CNS depression by reserpine appears to differ within the first few hours from that occurring later, when reserpine is supposed to have been completely metabolized.

Department of Pharmacology and Toxicology, Dartmouth Medical School, Hanover, N. H.

480 Netz, Björn, Carl-Otto, & Bergquist, Siwart. Effects of lysergic acid diethylamide (LSD-25) on normal subjects in a schizophrenia-discriminating test battery. Scandinavian Journal of Psychology, 1963, 4, 143-148.

Psychological tests with differing sensitivity to schizophrenic reactions were administered to eight normal subjects after oral intake of 75-100 μg LSD-25. Control data were obtained from placebo trials. Six of the tests (distinguishing intonation, sound effects, simple reaction time, disjunctive reaction time, apparent motion, and picture arrangement) were chosen as sensitive to schizophrenic reactions, two tests (synonyms and figure ground) were chosen as so-called hold tests, and another test (tone counting) was chosen as a measure of attention which is supposed to be reduced by LSD. Significantly lower results were obtained on 4 of the 6 sensitive tests after LSD, on one of the "hold" tests and on the attention test. The t-test was used for testing the significance of paired differences. Results of the ratings of the S-scale indicate that the majority of subjects experienced a more or less temporary euphoric reaction, while anxiety and depression were less common.

Psychological Laboratory, Beckomgerga Hospital, Bromma, Sweden

481 Resnick, O., Krus, D., Raskin, M., & Freeman, H. The effects of orally ingested l-tryptophan in MAO inhibited subjects. Federation Proceedings, 1963, 22, 510. (Abstract)

Four normal male subjects were given l-tryptophan orally (50 mg/kg) following several weeks of treatment with isocarboxizid (50 mg/day), 2/nialamide (100 mg/day), 3/nialimide (200 mg/day) and 4 a placebo. The neurologic CNS and behavioral effects following the oral administration of 50 mg/kg of l-tryptophan were very markedly potentiated in these 4 normal subjects by pretreatment with these MAO inhibitors.

Worcester Foundation for Experimental Biology, Shrewsbury, Mass.

482 Mennear, J. H., Clark, R., Samuel, G. K., Joffee, M. H., & Kodama, J. K. The comparative psychopharmacologic effects of scopolamine and atropine. Federation Proceedings, 1963, 22, 567. (Abstract)

The psychopharmacologic effects of i.v. administration of scopolamine and atropine were compared in monkeys trained to avoid or escape electric shock by responding to the position of a visual stimulus (Visual Discrimination Test or VDT), and in dogs trained either in a multiple stimulus conditioned avoidance response test (MSCAR) or a sustained physical exercise test (SPE). In the VDT, scopolamine impaired avoidance discrimination at a dose of 0.03 mg/kg while at a dose of 0.1 mg/kg both avoidance and escape discrimination at 1.0 mg/kg. In the MSCAR, doses of 1.0 mg/kg of scopolamine or 10 mg/kg of atropine were required to abolish avoidance behavior. In the SPE, 0.1 mg/kg of scopolamine significantly decreased the running time of dogs while 3.0 mg/kg of atropine was required to produce a similar effect. Scopolamine was approximately 10 times more potent than atropine in the VDT and MSCAR and approximately 30 times more potent in the SPE. Scopolamine in the SPE was found to be more potent than d-tubocurarine.

Hazelton Laboratories, Falls Church, Va.

483 Collins, R. J. Potency of dihydromorphinone, methadone and codeine compared to morphine in self-maintained addict rats. Federation Proceedings, 1963, 22, 248.

The use of i.v. drug administration as a positive reinforcement of lever pressing response in the rat has been reported by Weeks (1962). A method for comparing potency of narcotic analgesics to morphine and initial results with three agents is presented. Rats with right heart cannulas wore a saddle attached to a swivel which permitted i.v. injections while relatively unrestrained. After physical dependence to morphine was induced by hourly injections, rats quickly learned to press a lever switch to receive morphine. A balanced Latin square design consisting of 2 doses of standard (morphine 10 and 3.2 mg/kg injection) and 2 doses of test agent was used. Data were evaluated by a number

of effect metameters of which log of injection rate resulted in the most satisfactory assay. Potency estimates and fiducial limits by the method were: dihydromorphinone = 10 (5.2-19) x morphine; methadone - 2.4 (2.7 - 4.6) x morphine, and morphine - 1.5 (1.0 - 2.2) x codeine.

The Upjohn Company, Kalamazoo, Mich.

484 Keeler, Martin H., & Lipton, Morris A. Relations among effects of psilocybin on hallucinatory activity, critical frequency of fusion, and psychological disturbance. Federation proceedings, 1963, 22, 509.

Ingestion of psilocybin induces hallucinations that have at least partial origin in retinal processes. It was attempted to ascertain if these sensory phenomena were accompanied by changes in photopic foveal CFF (critical frequency of fusion), a more objective parameter of retinal function. The degree of hallucinatory activity, as determined by a questionnaire developed for this purpose, and the extent of CFF increases correlated among 12 subjects at the $p<.01$ level between 90 and 120 minutes after the administration of .2 mg of psilocybin/kg of subject body weight. CFF itself increased at the $p<.05$ level subject to limitations in the experimental procedure. These hallucinations and CFF increases may reflect common underlying alterations in the visual system and/or the coincidence of hallucinatory activity with anxiety. It is of interest that increases in the schizophrenic scale but not in the anxiety scale of a standard psychological test (MMPI) also correlated with hallucinatory activity and CFF increases at the $p<.01$ level.

University of North Carolina School of Medicine, Chapel Hill, N. C.

485 Koella, Werner P., Beaulieu, Roger F., & Bergen, John R. Effect of LSD-25 on the walking activity and pattern in the goat. Federation Proceedings, 1963, 22, 627. (Abstract)

The influence of two different doses of LSD (15 and 7.5 µg/kg body weight i.v.) on the goat was investigated in a modified open field test. In the larger dose and, to a lesser degree, in the smaller dose the drug increased the walking activity, measured as total walking distance per time unit. Under the influence of this psychotomimetic, the animals developed pronounced walking stereotypic patterns manifested by "squaring" (i.e., walking along the wall of the experimental room) or by other forms such as small rectangles, circles, figure eights, or L's. Any one of these patterns was found to be specific for a particular goat; every animal reacted with the very same pattern each time LSD was administered. These effects usually appeared within 5-10 minutes after the administration of the drug and abated within 60 minutes thereafter. With repeated injections at interval of 1-3 days, tolerance to the drug developed. Female goats were found to be more sensitive to the drug than males.

Worcester Foundation for Experimental Biology, Shrewsbury, Mass.

486 Keasling, H. H., Russell, R. R., & Triezenberg, H. J. The overt effects of tryptamine and their antagonism in the mouse. Federation Proceedings, 1963, 22, 624.

The i.v. administration of sublethal doses of tryptamine in Carworth male mice produces 4 readily observed responses: head weave (side-to-side searching (?) movements, ED_{50} 32 mg/kg; hind-leg spread (extension of the hind legs at approximately 45° from the trunk, ED_{50} 40 mg/kg); arched back (a peculiar hunching of the back, ED_{50} 48 mg/kg); and fore-paw clonus (bilateral placing movements, piano playing, ED_{50} 46 mg/kg). These symptoms are antagonized by the opiates (morphine, methadrome, codeine) as well as the

enothiazines (chlorpromazine, perphenazine, uphenazine). A variety of standard drugs es not antagonize these symptoms (doses low those producing gross neurotoxicity). spite of the similarity among the ED_{50}'s r the symptoms, the phenothiazines block e head weave and fore-paw clonus much more fectively. Opiates block all symptoms th little differential effect.

e Upjohn Co., Kalamazoo, Mich.

7 Boff, Edward, & Heise, George A. tenuation of tetrabenazine "reversal" by lordiazepoxide hydrochloride. Feder- ion Proceedings, 1963, 22, 510.

en a standard 2.0 mg/kg s.c. dose of trabenazine hydrochloride (TBZ) is admin- tered to rats in a 2-lever continuous oidance situation, depression of lever essing occurs within 20 minutes and lasts r 4 hours. Pretreating the rats with a haviorally inactive dose of iproniazid osphate (40 mg/kg s.c.) given 4 to 16 urs before TBZ "reverses" the usual TBZ fect: there is rapid lever pressing stimulation") for an hour following TBZ jection, followed by about 3 hours of owly declining response rate and finally dation (1960). When chlordiazepoxide given 2 hours prior to TBZ, the reversal TBZ by iproniazid is attenuated. The ration of lever pressing after TBZ in- ction is reduced from 4 to approximately 5 hours, and there is no stimulation. e minimum dose of chlordiazepoxide that tenuates TBZ reversal (0.45 mg/kg i.p.) much less than the minimum dose of lordiazepoxide (13 mg/kg i.p.) that de- reases avoidance rate when given alone. lorpromazine, meprobamate, and pheno- rbital, in contrast, attenuate TBZ reversal ly at doses that also depress avoidance te when given alone. Chlordiazepoxide locks the depression of avoidance rate roduced by 3,4-dihydroxyphenylalanine, 00 mg/kg i.p., but not the depression pro- uced by 5HTP, 200 mg/kg i.p.

offman-LaRoche Inc., utley, N. J.

488 Boggs, D. E., & Polidora, V. J. Biochemical and behavioral observations of phenylketonuria (PKU) in rats. Federation Proceedings, 1963, 22, 515. (Abstract)

Biochemical and learning data from a series of 9 experiments (172 rats) support the following conclusions and interpretations: 1) Learning tests employing water deprivation produced equivocal results presumably due to the decreased food intake and resultant hypermotivation of PKU rats. 2) In learning a swimming maze, however, PKU rats on a 7% phenylalanine (PA) diet from weaning to 72, 87, or 90 days of age were significantly poorer than controls. 3) Rats on 7% PA from weaning to 42 days learned as well as pair-fed or ad lib controls, but when kept on diet to 56 days, they were poorer than both. 4) Learning ability did not correlate with blood PA (decreased with time on diet), liver PA hydroxylase (remained at 50%), or PA-pyruvic transaminase (only slightly depressed), suggesting that these enzymes may have been adequate to metabolize the reduced PA/body weight intake in older rats. 5) Behavioral effects of PKU can be reliably induced in rats by 7% PA from weaning 53-90 days of age.

Department of Pediatrics, University of Wisconsin Medical School, Madison, Wis.

489 Schwartz, Arthur S. Effects of LSD on evoked potentials and behavior in the conscious cat. Federation Proceedings, 1963, 22, 627. (Abstract)

The effect of low (10-35 mg/kg) and high (1 mg/kg) LSD doses on amplitude of visual and auditory evoked responses and the gross sensory responsivity of conscious cats was assessed. Responses were compared to the mean pre-injection amplitude, and then pooled for each particular structure and dose level for comparison to the mean amplitude of the response after saline injection. The results for low LSD doses showed increased variability of response amplitude in all areas monitored (auditory

and visual cortices, lateral geniculate body, and cochlear nucleus), and a slight increase in amplitude of geniculate responses only. Behaviorally, auditory and visual responsiveness increased slightly. After high LSD doses, cortical responses were enhanced, while subcortical responses were depressed. Behaviorally, auditory responsivity markedly increased while visual responsivity was depressed. Lack of agreement between aspects of the behavioral and electrophysiological data may reflect a differential function of cortical versus subcortical centers of the two sensory systems, or the fact that evoked potential amplitude in the above areas bears little or no relation to the differential behavioral effects of LSD, and that other response parameters or other neutral areas are involved.

St. Elizabeth's Hospital, Washington, D. C.

490 Cluxton, J. F. Modifying effect of stress on LSD disruption of performance in rats. Federation Proceedings, 1963, 22, 510. (Abstract)

LSD alters the performance of a learned task in rats. The influence of stress on the performance-modifying effect of LSD was investigated. Time and number of errors in running the L-III maze were used as a measure of performance. Fourteen female rats were equally divided into control (C) and experimental (E) groups and trained to run the maze. The 2 groups were treated alike except that E group received shock 5 times/day for 6 days. The shock was preceded by a signal light using a constant time sequence. On the test day, animals of both groups received 0.2 mg/kg i.p. of LSD. E group was then shocked for five cycles. Ten minutes after injection all rats were tested in the maze. The C group's time (mean sec ± S.E. mean) increased from 4 ± 0.2 to 388 ± 25 and errors from 0 to 7 ± 0.6. The E group's time increased from 4 ± 0.2 to 37 ± 13 and errors from 0 to 1 ± 0.6.

Department of Pharmacology and Therapeutics, University of Florida College of Medicine, Gainesville, Fla.

491 Battig, K. Die Wirkung von Training und Amphetamin auf Ausdauer und Geschwindigkeit der Schwimmleistung der Ratte. (The effect of training and amphetamine on the endurance and speed of the rat's swimming performance.) Psychopharmacologia, 1963, 4, 15-27.

The effects on swimming performance of a 7-day training period and a subsequent application of 1.5, and 4 mg/kg amphetamine were measured in 4 groups of 10-12 rats each. In group 1, endurance was measured until the rats sank 40 cm below the water surface. In group 2, endurance was measured until the rats were breathing out 40 cm below the water surface. In these two groups, training did not improve performance; 1.5 mg/kg amphetamine produced a small and nonsignificant improvement and 4 mg/kg amphetamine produced an improvement which was significant for both groups together. In group 3, the rats had to swim 10 times in a row toward an escape ladder situated at the end of a water alley. In group 4, the task was essentially the same; however, the rats had to lift a load of a set of pulleys by pulling at the thread attached to their tail, while swimming toward the escape end of the alley. Training produced in group 3 a small improvement of swimming speed and in group 4 a considerable one. Amphetamine had no effect in group 3 and produced in group 4 an impairment which was highly significant for the swimming condition with pulling the load and just below the level of significance for the condition without pulling the load. These opposite effects of amphetamine on endurance and speed of swimming are discussed in terms of the different requirements of the two behavioral tasks.

Institut für Hygiene und Arbeitsphysiologie Eidgen. Technische Hochschule, Zurich, Switzerland

2 Huffman, Warren J., Florio, Aurelio
, Payne, Jobe L., & Boys, Floyd E.
e influence of two selected tranquilizers
driving skills. American Journal of
ychiatry, 1963, 119, 885-886.

enty-five student volunteers were studied
test the behaviorial effects of normal
double the normal dosage of hydroxy-
enamate (Listica) on reaction time,
sual acuity, and hand steadiness. Each
bject served as his own control. The
blets were administered 1 hour before
sting. Some 16 measurements were re-
rded for each subject on 6 occasions--
ter placebo, after hydroxyphenamate
00 mg), after meprobamate (400 mg and
0 mg). Since this was a multivariable
udy and some statistically significant
fference would be expected by chance, the
thors concluded that under conditions
their experiment hydroxyphenamate had
significant effect on performance at
e normal or double the normal dosage.

iversity of Illinois, Urbana, Ill.

3 Uhr, Leonard, Platz, Arthur, &
ller, James G. Time and dosage effects
meprobamate on simple behavioral tasks.
urnal of General Psychology, 1963, 68,
7-323.

me 16 male paid volunteers, 21 years and
der, were tested under placebo and 3
sages of meprobamate (400, 800 and 1,600
) to determine response curves over a
hour-test period. Each subject served
his own control; 2 additional runs under
acebo and 1,600 mg of meprobamate were
nducted to control for possible diurnal
ffects. Analysis of scores on 4 psycho-
tor tests and 3 personality checklists
owed that on the 5th cycle, 1½ hours
ter ingestion, there was no evidence
at subjects performed differently under
ximum drug dosage than under placebo.
gnificance tests between preingestion as
mpared to postingestion drug performance
r the maximum drug dosage showed no con-
istent drug effects. Comparison of these changes under placebo confirmed this finding. Placebo runs showed changes in performance through the 4-hour-period as large as the dose runs.

Mental Health Research Institute
University of Michigan, Ann Arbor, Michigan

494 Chen, Graham, Bohner, B., & Bratton, A. C., Jr. The influence of certain central depressants on fighting behavior of mice. Archives Internationales de Pharmacodynamie et de Therapie, 1963, 142, 30-34.

A comparative study of the suppressive activities of meprobamate, phenobarbital, carbromal, chloral hydrate and trichloramate in foot shock-induced fighting episodes in albino mice. The mice were preconditioned with a 3-minute-period foot shock before test to eliminate the necessity of selecting the responsive animals. The drugs were administered orally to fasted mice and tested at the time of their predetermined peak effect. Their ED_{50}s' were found to be approximately the same as those of the corresponding drugs required to produce maximal sedation. The suppression of the fighting reaction of mice was apparently due to a similar sedative action of these drugs.

Research Division, Parke, Davis & Co.
Ann Arbor, Michigan

495 Lawton, M. Powell, & Cahn, Burton. The effects of diazepam (Valium) and alcohol on psychomotor performance. Journal of Nervous and Mental Disease, 1963, 136, 550-554.

Some 20 male paid volunteers were given a battery of 4 psychological and psychomatic tests on the fourth day of medication under each of 4 treatment conditions: 1) placebo pill - placebo drink; 2) placebo pill - alcohol; 3) diazepam - placebo drink; and 4) diazepam - alcohol. Each subject was tested under each of the four conditions in a replicated Latin square design. Tests

administered were a cancellation test, a digit symbol test, an addition test, and a pegboard placement test. Results show a small, but statistically significant tendency for psychomotor performance to be influenced with Valium medication whether with alcohol or placebo. There was no evidence to suggest a potentiating decrement of performance with a combined dosage of diazepam and alcohol.

R.D. #2, Collegeville, Pennsylvania

496 Finocchio, D. V. Drug effect on "emotionally" disrupted timing behavior. Federation Proceedings, 1963, 22, 511. (Abstract)

These studies were designed to assess effects of several drugs on changes produced in a temporal pattern of responding by presentation of conditioned emotional stimuli. Timing behavior was established by requiring rats to space their lever-pressing responses by intervals of at least 18" to obtain food. This reward schedule produced a low rate of responding with an average 20" interval between responses. Presentation of the emotional stimuli disrupted this temporal pattern; the rats responded at a higher rate and at intervals less than 18". Low doses of ethyl alcohol and Su-8842, the methyl ether of methyl reserpate, attenuated the emotional effect of the stimuli resulting in a lower response rate and a lengthening of the interval between responses. High doses were disruptive resulting in irregular patterning and periods of no responding. Methamphetamine and chlordiazepoxide consistently increased the rate shortening the average interval between responses to less than 18". Chlorpromazine reduced the number of responses but had little effect on their temporal spacing except at the highest dose where an irregular pattern emerged. In summary, emotional stimuli produce disruptive effects on timing behavior which can be attenuated with ethyl alcohol and Su-8842.

Research Department, CIBA Pharmaceutical Co., Summit, N. J.

497 Costello, C. G. The effects of depressant and stimulant drugs on the relationship between reaction time and stimulus light intensity. British Journal of Social and Clinical Psychology, 1963, 3, 1-5.

It was predicted on the basis of Pavlovian theory and results with schizophrenics, that both 10 mg of amphetamine (by increasing the normal subject's level of excitation) and 194 mg of sodium seconal (by decreasing his level of excitation) would result in the paradoxical increase in reaction time (RT) with an increase in stimulus intensity. Five groups of 8 college students were tested after one of the following treatments: 10 mg of amphetamine, 194 mg of seconal, 800 mg of meprobamate, placebo tablets, and no drug. Their RT's to light of 8 intensities (increasing from 16 ft. candles to 1,500 ft. candles) were determined. The predictions were not confirmed. The seconal, meprobamate, and placebo groups produced significantly different RT from the amphetamine and no drug groups which did not differ in their mean RT.

Regina Psychological Laboratory, Monroe Wing, Regina, Saskatchewan, Canada

498 Meyer, Patricia M., Horel, James A., & Meyer, Donald R. Effects of dl-amphetamine upon placing responses in neodecortica cats. Journal of Comparative and Physiological Psychology, 1963, 56, 402-404.

Six cats with extensive lesions of the neocortex were tested for visual placing and left-and right-forepaw tactile placing responses before and after the administration of dl-amphetamine sulfate; 13 of 15 responses that had not returned after many months of postoperative recovery appeared and subsequently disappeared after drug injection. These results show that recovery is possible in animals that lack those regions of the neocortex that have been considered to be completely indispensable.

Ohio State University, Columbus, Ohio

Resnick, Oscar, Krus, Donald, Raskin,
lton, & Freeman, Harry. Reserpine action
subjects treated with monoamine oxidase
nibitors. Archives of General Psychiatry,
53, 8, 481-485.

ocarboxazid (Marplan) given for 2 weeks
llowed by a single i.m. injection of
serpine (Serpasil) potentiated the seda-
ve and tranquilizing effects of reserpine
le nialamide (Niamid) and a single i.m.
jection of reserpine markedly attentuated
l delayed the effect of reserpine. Experi-
nts reported here represent an attempt
indirectly assess the influence of
ychoactive drugs on the CNS of man. Six
rmal male subjects were treated with
ocarboxazid (50 mg daily) for 2 weeks and
en given a single i.m. injection of 1.25
reserpine. Though the beneficial effects
reserpine were potentiated, the side
fects, such as headache, nasal congestion,
onchial constriction, miosis, bloodshot
es, gastritis, and lowering of blood
essure were accentuated. A fall in the
parent eye horizon (AEH) was noted. It
s no longer biphasic. The reason for
ese effects could be buildup of serotonin
oth central and peripheral) but no similar
ildup of the catecholamines. In a second
st, three of the same subjects were given
alamide (100 mg daily) for 2 weeks,
llowed again by a single i.m. injection
1.25 mg reserpine. The typical biphasic
sponse of reserpine on the AEH was observed
d no lowering of blood pressure was
ticed. Preliminary analysis of tests with
hizophrenic patients indicate that pre-
eatment with iproniazid, isocarboxazid
d phenelzine may also potentiate the
mpatholytic and sedative effects of
serpine.

rcester Foundation for Experimental
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rcester, Massachusetts

500 Pearson, John W., & DeKornfeld, Thomas J. Effect of methotrimeprazine on respiration. Anesthesiology, 1963, 24, 38-40.

Healthy adult male volunteers showed no significant respiratory depression from 15 mg i.m. methotrimeprazine, while 10 mg i.m. morphine sulfate and a combination of both caused depression of the respiratory system. The results of this study indicate that methotrimeprazine causes respiratory depression when room air was being breathed, but not with a mixture of six percent carbon dioxide in room air. The drowsiness and sedation produced by this phenothiazine derivative cause a diminution of alveolar ventilation when this is not being strongly stimulated. Six percent carbon dioxide presents a potent stimulus, which the action of methotrimeprazine is not strong enough to overcome. This drug does not significantly potentiate the respiratory depressant action of the morphine, though it potentiates the sedation.

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501 Valette, G., & Raunaud, G. Action of phenothiazine derivatives on the audiogenic crisis in mice. In Centre National de la Recherche Scientifique. Psychophysiologie, neuropharmacologie et biochimie de la crise audiogene. (Psychophysiology, neuropharmacology, and biochemistry of the audiogenic seizure.) Paris, Centre national de la Recherche Scientifique, 1963.

The influence of various therapeutic groups of phenothiazine derivatives on the audiogenic seizure of the mouse was studied in animals of susceptible strain. Convulsions were released by a complex sonic stimulus. Some phenothiazine derivatives inhibit audiogenic seizure. The most active are levomepromazine, chlorpromazine, and methopromazine; all of them have a typical neuroleptic action in human medicine. Alimenazine and aminopromazine are less active on audiogenic seizure. Thioproperazine and prochlorperazine aggravate the convulsion and increase the ratio of death in seizures in a large number of animals. Like reserpine they have a strong experimental catatonizi action and clinically bring about secondar extrapyramidal manifestations. It appears that there is a relation between increase of the audiogenic seizure, experimental catatonizing action, and frequency of extrapyramidal manifestations in human medicine.

(No address)

502 Mercier, J. Modification of the audi genic seizure of albino rats under the influence of various pharmacodynamic agents. In Centre National de la Recherche Scienti que. Psychophysiologie, neuropharmacologi et biochimie de la crise audiogene. (Psychophysiology, neuropharmacology, and biochemistry of the audiogenic seizure.) Paris: Centre National de la Recherche Scientifique, 1963.

Audiogenic seizure of the albino rat (ASAR is a fragile phenomenon which is not epileptic. Drugs which depress nervous activity (anticonvulsants, neuroplegics, hypnotics, spinal cord depressants) suppre ASAR strikingly. However, some neurostimu lants which exert stimulation upon the reticular formation (epinephrine, ephedrin amphetamine) afford good protection; hallu cenogenic drugs likewise produce weak activity. The protecting action of atropi or the sensitizing action of physostigmine and nicotine may be due to their influence on the CNS. Lack of epinephrine release would permit audiogenic seizure in some sensitive, nonemotive animals, whereas several nonbiological sympathomimetic drug suppress audiogenic seizure of the albino rat.

(No address)

Swinyard, E. A. Some physiological
perties of audiogenic seizures in mice
their alteration by drugs. In Centre
ional de la Recherche Scientifique.
chophysiologie, neuropharmacologie et
chimie de la crise audiogene. (Psycho-
siology, neuropharmacology, and bio-
mistry of the audiogenic seizure.) Paris:
tre National de la Recherche Scientifique,
3.

patterns of maximal seizures induced in
e and supramaximal electroshock,
razol, or sound, except for latency and
d running, are remarkably similar. The
vulsant effects of sound were studied in
diogenic-seizure-susceptible mice (MASS).
MASS group included animals which uni-
rmly responded with a tonic-clonic seizure,
the submaximal audiogenic-seizure-
sceptible mice (SASS) exhibited either
izures of less severity or no response.
razol did not change the sensitivity.
methadine, phenobarbital, diphenylhydan-
in, and meprobamate prevent maximal audio-
ic and maximal electroshock seizures in
ntoxic doses, whereas chlorpromazine and
serpine do not. The effective drugs are
least three times more potent against
ximal audiogenic seizures than against
ximal electroshock seizures.

address)

DiMascio, Alberto, Havens, Leston L.,
Klerman, Gerald L. The psychopharmacology
phenothiazine compounds: a comparative
udy of the effects of chlorpromazine,
omethazine, trifluoperazine and perphena-
ne in normal males. I: Introduction, aims,
d methods. Journal of Nervous and Mental
sease, 1963, 136, 15-28.

is study investigated three aspects of the
armacology of phenothiazines in normal
man subjects. These were: 1) the para-
ters of phenothiazine actions, particularly
e temporal course of drug effects, the dose-
sponse relationships, and the diversity of
e drug effects; 2) the possible relation-
ips between the chemical structure of
enothiazines and their actions upon
ecific psychophysiological and performance
nctions; 3) the drugs' effects upon
ysiological and performance functions in
relationship to their differential therapeutic efficacy. Four phenothiazine derivatives (two aliphatic compounds--chlorpromazine and promethazine), and two piperazines (perphenazine and trifluoperazine) were examined, each at 4-dosage levels. A double-blind procedure was used, and the effects of a single oral dose were recorded on a battery of physiological, psychological and subjective response measures. One of the more interesting initial findings was that all four drugs reached their maximal effect at the fourth hour after administration.

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505 DiMascio, Alberto, Havens, Leston L., & Klerman, Gerald L. The psychopharmacology of phenothiazine compounds: a comparative study of the effects of chlorpromazine, promethazine, trifluoperazine, and perphenazine in normal males. II: Results and discussion. Journal of Nervous and Mental Disease, 1963, 136, 168-186.

Based on clinical experience and using chlorpromazine as a prototype, the available conceptions as to what effects are related to therapeutic efficacy, do not seem to be generalizable to other agents, nor perhaps, are they valid even for chlorpromazine. The degree to which the effects of chlorpromazine, promethazine, trifluoperazine and perphenazine were exhibited in this extensive study was a joint function of the particular drug and dosage employed. At peak time of action chlorpromazine produced psychomotor inhibition, mental confusion, autonomic alterations and hypnosis. Perphenazine and trifluoperazine had similar effects. Perphenazine and trifluoperazine produced only minimal changes in all of these measures, and in contrast, at certain dose levels, induced psychomotor stimulation and a statistically significant improvement in speed of performance on cognitive tasks. The aliphatic phenothiazines, chlorpromazine and promethiazine and the piperazine phenothiazines, perphenazine and trifluoperazine, differed

markedly in their effects on a variety of test measures, and the differences increased as the dosage increased. Of the many effects observed, i.e., psychomotor inhibition, mental confusion or retardation, autonomic nervous system changes and hypnosis--none seemed to be the key, or common denominator, in differentiating effective agents from the ineffective ones.

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506 DiPalma, Joseph R. The basic pharmacologic principles underlying the use of sedatives and tranquilizers. Clinical Pediatrics, 1963, 2, 225-232.

Upon establishing a rational basis for clinical use of sedatives and tranquilizing drugs, one is impressed by the time-tested reliability and predictability of the barbiturates. It is the purpose of this review to restate the basic pharmacologic principles underlying the clinical use of sedatives and tranquilizers. The pharmacological agents discussed are grouped into 1) ions, alcohols and aldehydes, 2) urea derivatives, 3) antihistamines, 4) Rauwolfia alkaloid derivatives, 5) substituted phenothiazines, 6) atropine groups and a new clinical group which includes the popular chlordiazepoxide (Librium). The reliability, safety, and limited therapeutic range of the ionic, alcoholic and aldehyde group is discussed. The urea derivatives, highlighted by the barbiturates, are given much support as the most efficacious CNS depressant available. The recent popularity of the phenothiazines is revealed, although the side effects are felt to be quite pronounced and unpredictable by the authors. A specific request is made to limit the use of phenothiazines in pediatric practice especially in control of vomiting. The endocrine and metabolic effects of the Rauwolfia alkaloid derivatives were restricting the use of these agents. Among the less potent drugs, meprobamate, the antihistamines and their close relatives, perhaps satisfied most a need for CNS depressants not adequately served by barbiturates. Generally speaking, in selecting a sedative or tranquilizer, nothing is more valuable than an accumulated experience and knowledge about the drug and in this respect the barbiturates have withstood the test of time.

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507 Swaine, Charles R. Effect of adrenergic blocking agents on tyramine-induced release of catecholamines from the cat heart. Proceedings of the Society for Experimental Biology and Medicine, 1963, 112, 388-390.

Alpha-adrenergic blocking agents like phenoxybenzamine are demonstrated to be capable of interfering with the release of catecholamines induced by sympathomimetic amines. The purpose of this paper is to determine the effect of alpha-adrenerg blocking agents on the release of catecholamines induced by sympathomimetic amines. The general procedure employed for the investigation involved the study of catecholamine release in the isolated perfused cat heart. The alpha-adrenergic agents used in the study were phenoxybenzamine, GD-131, phentolamine and dihydroergotamine. In some cases a catecholamine releasing ager such as tyramine was used to utilize its ability to release fluorometrically determin able amounts of catecholamines in an isolate perfused cat heart preparation. The studies revealed that the release of catecholamines produced by tyramine in the isolated cat heart is inhibited by phenoxybenzamine and GD-131 but not by phentolamine or dihydroergotamine. The possibility that beta-haloalkylamines interfere with the release of catecholamines in vivo, as well as inhibiting the effects of catecholamines on effector cells, is strongly suggested by this investigation.

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Bondarev, M. G. Vliyaniye analept-
v na bul'barnyy sosudodvigatel'nyy
ntr. (The effect of analeptics on the
bar vasomotor center.) In: Val'dman,
V. (Ed.), Aktual'nyye problemy farma-
logii retikulyarnoy formatsii i sinapti-
skoy peredachi. Leningrad: I Lenin-
dskiy Meditsinskiy Institut imeni
demika I. P. Pavlova, 1963, Pp. 216-236.

nges in blood pressure evoked by analep-
s are due to their effect on a vasomotor
ter of the medulla oblongata. Spinal
omotor centers play an important role
blood circulation. The majority of
eriments were carried out on 100
erebrated cats; some experiments were
ried out on intact or bulbar (transection
ng a lower edge of the pons) animals.
polar stimulation lasting 15 seconds was
ieved by means of nicochrome-insulated
ctrodes. Five analeptics were administered
ravenously. Caffeine (5-20 mg/kg),
tylenetetrazol (5-20 mg/kg), Coramine
20 mg/kg), strychnine (0.001-0.02 mg/kg),
securinine (0.005-0.02 mg/kg) increased
pressor reaction by approximately
30 percent when the reticular microcellular
leus was stimulated. Only caffeine and
tylenetetrazol increased the responses
m vestibular nuclei. Caffeine distinctly
ibited reactions from a descending path,
le pentylenetetrazol, strychnine and
urinine increased reactions, whereas
amine had no effect on them. In other
es analeptics inhibited the vascular
actions and decreased mostly the depressor
actions. The effect of analeptics on
scular reactions depended not only on the
ructure, responsible for a pressor
epressor) reaction, and level of the brain
ansection, but also on the dosage.

address)

509 Kovalev, G. V. Lokalizatsiya i kharakter deystviya nekotorykh neyrotropnykh sredstv na bul'barnyy sosudodvigatel'nyy tsentr. (The localization and mode of action of some neurotropic drugs on the bulbar vasomotor center.) In: Val'dman, A. V. (Ed.), Aktual'nyye problemy farmakologii retikulyarnoy formatsii i sinapticheskoy peredachi, Leningrad: I Leningradskiy Meditsinskiy Institut imeni Akademika I. P. Pavlova, 1963, Pp. 237-265.

Neurotropic drugs suppressed pressor reactions from various components of the medulla oblongata and pons varolii to a different extent: first, response reactions from the vestibular nuclei were reduced, then pressor effects from the lateral reticular structures were suppressed and finally, pressor reactions from the medial reticular nuclei were reduced. The experiments were carried out on decerebrated and decerebellated cats. Pons varolii and medulla oblongata were locally stimulated at different points. Vascular reactions were recorded by a standard method described before. Among narcotics, Nembutal (pentobarbital sodium) and urethan, not only suppressed vasomotor reactions to a different extent, but also had a different effect on the latent period of the onset of vascular responses. The effect of morphine and promedol on pressor reactions varied and depended on the characteristics of different formations. In these experiments vascular reactions, under the effect of chlorpromazine and DG-ergotoxine, decreased depending on the location of the stimulating electrode. Amizil (benactyzine) and scopolamine in doses of 0.1-0.5 mg/kg suppressed depressor reactions, by 30 percent. DG-ergotamine was most effective in suppressing response reactions, chlorpromazine was less effective, whereas scopolamine and amizil were the least effective.

(No address)

510 Buryak, M. A. Vliyaniye neyrotropnykh sredstv na eksperimental'nyye aritmii, vyzvannyye lokal'noy stimulyatsiyey bul'barnoy retikulyarnoy formatsii. (The effect of neurotropic drugs on experimental arrythmias evoked by local stimulation of the bulbar reticular formation.) In: Val'dman, A. V. (Ed.), Aktual'nyye problemy farmakologii retikulyarnoy formatsii i sinapticheskoy peredachi, Leningrad: I Leningradskiy Meditsinskiy Institut imeni Akademika I. P. Pavlova, 1963, Pp. 266-280.

Disorders of cardiac rhythm and coronary circulation are evoked not only by the interaction of different factors directly on neural elements of the heart and extracardial nerves, but also by the effect on different sections of the central nervous system. Seventy experiments were carried out on urethan-narcotized cats (1.0-1.2 mg/kg i.p.). After the cerebellum had been removed, the medulla oblongata was stimulated by means of unipolar electrodes for 5-10 sec. with an interval of 8-10 minutes. In case of ventricular extrasystole disorders, chlorpromazine (0.25-0.5 mg/kg) completely prevented these disorders; chloracisin (0.5-1.5 mg/kg) eliminated arrythmias and accompanying disorders of venous circulation; morphine (0.2-10 mg/kg) did not eliminate disorders of a cardiac rhythm and even increased extrasystole and bradycardia. Chlorpromazine (0.5-1.0 mg/kg) and chloracisin (0.5-3 mg/kg) suppressed sinus bradyarrythmias, whereas morphine (1-10 mg/kg) increased a delayed rhythm of cardiac contractions. Chlorpromazine (1-1.5 mg/kg) suppressed a development of supraventricular and ventricular paroxysmal tachycardia, while chloracisin (0.5-1 mg/kg) delayed the onset and duration of tachycardia. Different doses of chloracisin as well as chlorpromazine suppressed arrythmias. In all cases, morphine (0.5-10 mg/kg) alleviated the stimulating effect of different structures of the medulla oblongata, increasing a delayed cardiac rhythm, extrasystole, and other changes in the EEG.

(No address)

511 Forney, Robert B., Hughes, Frances, W. & Hulpieu, Harold R. Potentiation of ethanol induced depression in dogs by representative ataractic and analgesic drugs. Quarterly Journal of Studies on Alcohol, 1963, 24, 1-

In adult mongrel dogs, potentiation of ethanol, when given in conjunction with tranquilizers or other drugs, has been demonstrated. The dogs used in this study, three to five for each dose of the drugs, were given ethanol, phenaglycodol (Ultran) meprobamate (Miltown, Equanil), hydroxyzine (Vistaril, Atarax), chlorpromazine (Thorazine), reserpine (Serpasil, Sandril, Reserpoid), d-propoxyphene (Darvon), codeine and morphine. The symptomatology of varying doses was observed. At 1 g of ethanol per kg of body weight no symptom appeared. The symptoms produced by the ataractic drugs included general incoordination and "hindsway" tremors in the hind leg. Larger doses of hydroxyzine produced a convulsive pattern, while a "start reflex" was caused by morphine. Three to five dogs were then given 1 g ethanol per kg in conjunction with each of the drugs. It potentiated the effect of six drugs in the following order: >chlorpromazine >d-propoxyphene = morphine > meprobamate = phenaglyco > codeine > hydroxyzine. Ethanol antagonized the excited state produced by hydroxyzine and did not influence the effects of codeine. (8 Refs.)

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512 Val'dman, A. V., & Arushanyan, E. B. Vliyaniye anal'getikov na segmentarnoye i suprasegmentarnoye tormozheniye. (The effect of analgesics on segmental and supra segmental inhibition.) In: Val'dman, A. V. (Ed.), Aktual'nyye problemy farmakologii retikulyarnoy formatsii i sinapticheskoy peredachi, Leningrad: I Leningradskiy Meditsinskiy Institut imeni Akademika I. P. Pavlova, 1963, Pp. 281-305.

Analgesics, without interfering with the inhibitory process itself, block the transmission of inhibitory impulse through neuron of a reticular complex of the brain stem and descending propriospinal neurons. This

icle reviews results of the study carried
for several years on the effect of
lgesics on inhibition of the central
vous system. Even large doses of mor-
ne have no effect on latent and refractory
iods, as well as amplitude of monosynaptic
ponse and postactive intensification.
phine and promedol, in doses of 5-15
kg, do not substantially affect the
ibitory effect. Even very small doses
nicotine have a pronounced cholino-
etic effect on Renshaw cells. Morphine
s not inhibit the knee reflex evoked by
otine. Nembutal (pentobarbital sodium)
urethan inhibit the knee reflex to a
ferent extent. Strychnine usually
torts reciprocal inhibition. During
rasegmental inhibition, as well as seg-
tal inhibition of different spinal
lexes, analgesics effect the inhibition
hout disturbing the onset of excitatory
cesses in motoneurons.

address)

Skorobogatov, V. I. Tsentral'noye
stviye kurarepodobnykh veshchestv.
e central effect of curarelike drugs.)
Val'dman, A. V. (Ed.), Aktual'nyye
blemy farmakologii retikulyarnoy
matsii i sinapticheskoy peredachi,
ingrad: I Leningradskiy Meditsinskiy
titut imeni Akademika I. P. Pavlova,
3,Pp. 306-320.

ording to the majority of clinical and
erimental observations, the central
fect of curare and curarelike drugs
cking synaptic transmission, is not
nounced. A comparison of the effect of
arelike drugs on the EEG of unnarcotized
bits in acute experiments and of rabbits
h implanted electrodes in chronic experi-
ts, indicated that these drugs in doses,
cking the neuromuscular transmission
th artificial respiration) and also in
es providing natural respiration (chronic
eriments), increased insignificantly the
chronous background activity of the EEG
thout changing the bioelectrical reactions
the cortex to peripheral stimulation. A
w Soviet curarelike drug, paramion, in a
se of 0.1-0.15 mg/kg desynchronized
spontaneous cortical activity. Even very large doses of tubocurarine (4-5 mg/kg), diplacine (25-30 mg/kg), decamenthonium (0.1-0.2 mg/kg), and ditilin (0.5-1 mg/kg) had no effect on the amplitude of mono- and polysynaptic discharges of depressor, as well as pressor reflexes, and also on the lability of cerebrospinal centers.

(No address)

514 Waser, P. G., & Spengler, J. Die pharmakologische Beeinflussing von Hunger und Sattigung. (Pharmacological influence on hunger and its appeasement.) Schweizerische Medizinische Wochenschrift, 1963, 93, 90-92.

Symptomimetic and neuroleptic drugs were found to have the strongest anorectic action of various psychopharmacological drug groups tested for this effect. The drugs used on rats in previous experiments by other investigators were sympathomimetics, psychotomimetics, analeptics, antihistamines, hypnotics, neuroleptics and MAO-inhibitors. Rats had been deprived of food for 16 hours before they were intraperitoneally injected with the respective drugs. Their food intake within the first 2 hours was determined and that dose was defined which would reduce the food amount to one-half of the normal control-value within the time limit. It was found that an anorectic effect was not necessarily combined with excitation. Meprobamate and phenobarbital increased the food intake. Their site of action corresponds to the localization of related psychologic and biochemical brain-functions.

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Zurich, Switzerland

515 Leishman, A. W. D., Matthews, H. L., & Smith, A. J. Antagonism of guanethidine by imipramine. Lancet, 1963, 7272, 112.

Imipramine antagonizes the hypotensive action of guanethidine and bretylium in experimental animals, a fact which has also found clinical application. Three male hypertensive patients were treated with guanethidine. The addition of imipramine in dosage of 25 mg t.i.d. abolished the side effects of guanethidine but resulted in loss of blood pressure control. When imipramine was withdrawn blood pressure control reappeared but side effects such as diarrhea, nasal stuffiness and failure of ejaculation manifested themselves. Imipramine apparently antagonizes all effects of guanethidine due to adrenergic neurone blockade. It is, therefore, suggested that these two drugs in combination should best be avoided.

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Sheffield, England

516 Vulpe, M., Caldwell, D. F., & Rodin, E. Ontogenesis of Megimide seizures in the rat. Experimental Neurology, 1963, 8, 350-360.

The effect of bemegride (Megimide) was studied in 360 newborn and adult rats. Tonic extensor posture alternating with flexor relaxation was elicited in the newborn by 0.030 mg i.v. per g of body weight. In the 31-40 g rat the convulsant dose was 0.013 mg per g of body weight, and in adults the tonic-clonic seizures were produced by 0.005 mg per g of body weight. The authors suggest that the activation by Megimide of a low-threshold neuronal system patterns the seizures of autonomic behavior, while another neuronal system of higher threshold is responsible for the tonic-clonic convulsion. The slow dysrhythmic and high-threshold convulsion of the newborn rat gradually evolves into the low-threshold fast rhythmic and organized seizure of the adult, a change reminiscent of the development of the seizure pattern from lower vertebrates to mammals.

Lafayette Clinic
Detroit, Michigan

517 Forrest, Irene S., & Forrest, Fred M. On the metabolism and action mechanism of the phenothiazine drugs. Experimental Medicine and Surgery, 1963, 21, 231-240.

A pattern for physiological drug metabolism has emerged from the investigations of various specialized research laboratories even though the mode of action of the phenothiazines is still the subject of controver The usefulness of tests to determine phenothiazines and imipramine in urine is discussed, as well as the desirability for quantitative determination of urinary chlorpromazine. Data on the determination of chlorpromazine in tissues and speculatio on the action mechanism of phenothiazines are reviewed.

Veterans Administration Hospital
Palo Alto, California

518 Corne, S. J., Pickering, R. W., & Warner, B. T. A method for assessing the effects of drugs on the central actions of 5-hydroxytryptamine. British Journal of Pharmacology, 1963, 20, 106-120.

Injection of 5-hydroxytryptophan into mice produces a characteristic head twitch. For a given period of observation, this response may be observed quantitatively by observing the proportion of mice showing at least one head twitch, or by counting the number of head twitches for each mouse. A method (based on the quantal response) of investigating the effect of centrally acting compounds on the head-twitch respons is described. Evidence is presented that the head twitches are due to the central action of 5-hydroxytryptamine formed by decarboxylation of 5-hydroxytryptophan. Head twitches are not indicated by MAO inhibitors and by phenytoin. Antagonists tested include an inhibitor of decarboxylas antagonists of 5-hydroxytryptamine, some antihistamines, major tranquilizers, and analgesic and sympathomimetic drugs. Drugs which neither potentiate nor inhibit the response include barbiturates and minor tranquilizers. The method may be valuable

the preliminary examination of compounds
kely to have a central action.

partment of Pharmacological Research
rke, Davis & Company
nslow, Middlesex, England

) Irwin, Samuel. Influence of external
ctors and arousal mechanisms on the rate
drug tolerance development. Archives
ternationales de Pharmacodynamie et de
erapie, 1963, 142, 152-162.

s of both sexes were trained to make a
dle-jump avoidance response and were
n administered subcutaneous chlorproma-
ne. They were evaluated for their
tial response to drug and the extent of
erance development. The rate of tolerance
velopment to chlorpromazine was signifi-
tly accelerated by increasing the
ensity of the conditioned buzzer (CS)
unconditioned electroshock (US) stimulus
d in an avoidance study. At higher levels
CS or US, tolerance development was
ghtly more rapid in females than males.
"arousal-provoking" quality of the
perimental situation was presented as a
mary factor affecting behavior and the
sponse to drugs. The authors consider that
y diverse experimental findings and
olated observations (including their own
dy) can be reconciled, explained or
edicted from a consideration of this one
ctor.

partment of Neuropharmacology
nering Corporation
omfield, New Jersey

) Poldinger, W. Klinische Erfahrungen
dem Thiaxanthenderivat Clopenthixol
rdinol) in der psychiatrischen Pharma-
therapie. (Clinical experiences with a
iaxanthen-derivative clopenthixol
rdinol) in psychiatric pharmacotherapy.)
erapeutische Umschau, 1963, 20, 534-538.

e thiaxanthen derivative Sordinol with the
emical abbreviation clopenthixol is to be
sidered as a neuroleptic with a strong
lative and somniferous effect, also
fluencing hallucinations and the production
paranoid ideas--although somewhat less
pronounced and with a certain exhaustion of
this effect--and, because of the quick onset
of the response, primarily suitable also for
acute and urgent cases. As somatic simul-
taneous phenomena should be mentioned first
and foremost dyskinetic conditions--which,
however, are easily eliminated and prevented
with orphenadrine and ethybenzatropine--
and vegetative symptoms as well as local
irritation symptoms by intramuscular appli-
cation. Consequently our special questions
can be answered as follows: 1) The introduc-
tion of a piperazine ring into the side
chain of the thiaxanthen derivative
chlorprothixen causes no diminishing but
an intensification of the sedative and
somniferous effect, compared with the same
change at the side chain of the phenothiazine
derivative chlorpromazine, whereas the
so-called "anti-psychotic effect" is not
intensified considerably. However, it does
result in an accumulation of extrapyramidal
simultaneous phenomena, first and foremost
in the form of dyskinesia. 2) The replace-
ment of the N-atom in the tricyclic ring
pattern of the perphenazin by a C-atom
causes no significant decrease of the
neuroleptic effect and the extrapyramidal
simultaneous phenomena, compared with the
corresponding combinations with dimethyl-
amine propyl side chain, whereas for this
reason the occurrence of a thymoleptic
effect could not be made appreciable.
(Author summary)
Kantonalen Psychiatrischen Klinik
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Luzern, Switzerland

521 Sivadjian, J., Vautrin, Maurice, &
Matge, Helene. Proprietes neuroleptiques
et anhidrotiques du triperidol (R 2498).
(Neuroleptic and anhidrotic properties of
triperidol (R 2498)). Therapie, 1963, 18,
1279-1285.

Triperidol, at a dose of 15 mg per kg s.c.,
does not succeed in preventing epileptic
fits in the guinea pig provoked by s.c.
injection of 80 mg per kg of diethyl-
aminophenoxyethane administered 30 minutes
later. On the other hand, this injection
does away with the cataleptic state of
animals due to triperidol. Triperidol at
doses of 28.5 to 38 mg per kg s.c.
suppresses the activity of the sweat glands

of rats and mice. The duration of this anhidrotic action depends on the dose administered and varies from 20 minutes for the strongest dose to 75 minutes for the weakest. The local injection of acetylcholine administered s.c. in the hind foot of the animal, re-established perspiration, which continued to remain inhibited for the opposite foot.

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522 Sivadjian, J. Action de la chlorpromazine dur l'epilepsie experimentale et sur la transpiration. (On the action of chlorpromazine on experimental epilepsy and on perspiration.) Archives Internationales de Pharmacodynamic et de Therapie, 1963, 377-384.

Chlorpromazine, at a dose of 25 mg/kg s.c., does not suppress the convulsions provoked on the guinea pig by 100 mg/kg of diethylaminophenoxyethane administered in the same way. On the other hand, chlorpromazine, at a dose of 20 mg/kg, is capable of protecting the animal from the typical epileptiform convulsions produced by a dose of 75 mg/kg of the same convulsive substance. Chlorpromazine, at a dose of 25 mg/kg, administered on the mouse intraperitoneally, brings about a marked decrease in perspiration in the space of an hour. (Author summary)

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Paris 15, France

523 van Praag, H. M., & Leijnse, B. Die Bedeutung der Monoaminoxydasehemmung als antidepressives Prinzip, II. (The importance of MAO inhibition as an antidepressive principle, II) Psychopharmacologie, 1963, 4, 91-102.

The effect of some MAO-inhibiting hydrazines on the matabolism of exogenous 5-HT was investigated in 18 patients. These drugs were found to reduce the production of 5-HIAA after oral administration of 5-HT. This phenomenon was not in any way correlated with the development of the physical changes. Moreover, it is probably not brought about by blockage of MAO activity. A few alternatives to inhibition of MAO activity are discussed. Electroshock therapy--with the same indications as the above mentioned antidepressive agents--had no influence on the metabolism of exogenous 5-HT. In six of the seven patients with agitated depressions examined so far, the 5-HIAA production after administration of 5-HT, respectively, 5-HIAA was abnormally low (<25%). The quantities obtained increased in proportion as the agitation subsided, irrespective of the therapy applied. The possible causes of this phenomenon are discussed. The conclusion is reached that the theory from which the reasoning starts--according to which the revitalizing effect of antidepressive hydrazines is related to their MAO-inhibiting capacity--is to be regarded as unfounded. Stress is laid on the importance of testing other points of attack of these drugs, with regard to their psychopharmacological significance.

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Rotterdam, Holland

524 Laborit, H., Wermuth, C., Weber, B., Brue, F., Leterrier, F., Delcambre, J. P., Bertharion, G., & Baron, C. Premiere utilisation en therapeutique d'une molecule biologique a activit psychotrope. (First therapeutic utilization of a biological molecule with psychotropic action. Revue Agressologie, 1963, 4, 321-340.

Succinic semi-aldehyde (S.S.A.) produces little toxicity and acts chiefly on the CNS. In animals it produces a state of tranquilization without sleep, and with neither secondary neurologic symptoms nor a decrease in oxygen consumption. On the EEG it appears to decrease the intensity of the stop-reaction, and even suppress it These reactions are also found in humans, with no hypnotic effect. No behavioral or neurologic problems, or lapses in consciousness are produced, but rather a sens of well-being and release. With no marked effect on the normal EEG, S.S.A. intensifi and largely diffuses the light and localized alterations that seem to result from metabolic disturbances. Stereotactic stud of the cerebrally evoked potentials in animals shows a marked increase in amplitude of the cortical potentials and no

anges in potential in the hippocampus,
alamus, or the reticular substance.
nally, interesting therapeutic effects
some patients are reported, particularly
ose with Korsakoff's syndrome or akinetic
teness.

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pital Boucicaut
ris 15, France

5 Julou, L., Courvoisier, S., Ducrot, R.,
urnel, J., Bardone, M. C., Leau, O.,
Myon, J. Etude des proprietes pharmaco-
giques generales de la cyano-3[(hydroxy-4
peridyl-1)-3 propyl]-10 phenothiazine
propericiazine (8.909 R.P.). (A study
the general pharmacological properties
cyano-3[(hydroxy-4 piperidyl-1)-3
opyl]-10 phenothiazine or propericiazine
.909 R.P.).) Compes rendus des seances de
Societe de Biologie, 1963, 158, 1242-
47.

opericiazine, 8.909 R.P., a phenothiazine
rivative, has a powerful effect on the
ntral nervous system. All its effects
e more marked than those of chlorpromazine.
s antiserotonin activity in vitro in
e rat is superior to that of chlorpromazine.
s effects on the cardiovascular system
d on the autonomic nervous system are
mparable to those of chlorpromazine. It
s generally well tolerated by rats and
gs in tests which lasted a month. Its
ute toxicity effects in mice are similar
those of chlorpromazine.

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try-sur-Seine, France

526 Soulairac, A., & Soulairac, M.-L. Action de differentes substances neurotropes sur la neuro-secretion et la structure histologique de l'hypothalamus anterieur. (Action of various neurotropic substances on the neurosecretion and the histological structure of the anterior hypothalamus.) Actualities Endicronologiques, 1963, 3, 39-43.

The results presented show clearly the effects of neurotropic substances on the neuro-secretion of the hypothalamus and on the structure of the neuro-secretory neurons. The drugs considered here were chlorpromazine, reserpine, ipronazid and serotonin. Two conclusions can be drawn from the studies described: 1) the relative dissociation between the condition of the neuro-secretion and the histological structure of the neuro-secretory elements and 2) the apparently very great sensitivity of the nucleoli to the action of psychopharmacological agents. The various neurotropic substances act directly on certain cellular structures of the hypothalamus and these actions represent one of the physiological mechanisms with which these substances act on the endocrinological equilibirum and on the functioning of the central nervous system.

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527 Chaun'-gen, Ma, & Val'dam, A. V. Eksperimental'nyye materialy po farmakilogii bul'barnogo dykhatel'nogo tsentra. (Experimental data on the pharmacology of bulbar respiratory center.) In: Val'dman, A. V.(Ed.) Aktual'nyye problemy farmakologii retikulyarnoy formatsii i sinapticheskoy peredachi, Leningrad: I Leningradskiy Meditsinskiy Institut imeni Akademika I. P. Pavlova, 1963, Pp. 190-215.

Since respiration is centrally regulated by the interconnected activity of a large complex of varied nerve elements (even a bulbar respiratory center located in the reticular formation of the brain stem is not uniform), the effect of neurotropic drugs on the respiratory function has been studied on the basis of the type and extent of the effect of these drugs on definite morphological elements of the respiratory center. The experiments were carried out on the decerebrated cats. Two to three unipolar electrodes were implanted into different sections of the medulla oblongata. Stimulation was applied in series of 15 seconds. Response respiratory reactions were recorded pneumographically. All drugs were administered intravenously. Small doses of ethyl carbamate (50-100 mg/kg) and of Nembutal (0.5-1 mg/kg) completely inhibited the expiratory reaction. As the doses of the drugs were gradually increased, the amplitude of expiratory and inspiratory reactions was gradually inhibited. Morphine (0.5 mg/kg) delayed the rhythm of respiratory movement. but an additional dose of 1 mg/kg completely inhibited the expiratory reaction. Trimeperidine increased (0.25 mg/kg) the rhythm of inspiratory reaction, whereas an additional dose of 0.5 mg/kg completely inhibited the respiratory reaction. Morphine and trimeperidine in doses of 1-3 mg/kg considerably increased the amplitude of inspiratory and expiratory reactions; the amplitude remained unchanged when the dose of morphine was increased to 15 mg/kg. The effect of chlorpromazine on the respiratory reaction also depended on the site of stimulation. In the areas "sensitive" to chlorpromazine, the amplitude of respiratory reactions was decreased by 0.05 mg/kg of chlorpromazine, and the doses of 0.5-1 mg/kg usually completely (or almos completely) inhibited the respiratory responses. The effect of two analeptics, pentylenetetrazol and caffeine, varied. Small doses of pentylenetetrazol (0.5-1 mg/kg) inhibited the respiratory reaction. In the majority of experiments, caffeine had no effect on the respiratory reaction. Only in 3 cases caffeine in doses of 5-10 mg/kg increased the amplitude of respiratory responses when the area of descending pathways was stimulated. The doses of 5-10 mg/kg of pentylenetetrazol and 10-20 mg/kg of caffeine increased the rhythm of a background respiration; the stimulating effect of pentylenetetrazol was higher than the effect of caffeine.

(No address)

528 McGeer, Patrick L., Wada, Juhn A., & McGeer, Edith G. Correlations between central aromatic amine levels and behavioral tests following administration on psychoactive drugs. In: Wortis, Joseph (Ed.), Recent Advances in Biological Psychiatry, 5, New York: Plenum Press, Inc., 1963. Pp. 228-236.

Conditioned avoidance responses in cats show that enhancement of catecholamine and a decrement of serotonin can be correlated with an improvement in performance, while an enhancement in serotonin and a decrement in catecholamines can be correlated with a deterioration of performance. In the experimental studies reviewed, two precursor amino acids were used, DOPA, the precursor of the catecholamines, and 5-hydroxytryptophan, the precursor of serotonin. The psychoactive drugs were reserpine and iproniazid. The behavioral studies were carried out first, details being reported in another publication. The result of the behavioral studies are schematically summarized and details of brain dissection which followed are given. The central

matic amines, serotonin, dopamine, nor-
nephrine, and histamine were determined
ctrophotofluorometrically, recoveries
ng determined through recovery of a
ioactive tracer added to the analyzate.
pattern of amine changes with various
g treatments was generally similar from
brain area to another but differed
ntitatively. Those areas containing
lowest control concentrations of amines
the greatest tendency to increase their
ative levels after the load of percursor.
as containing the highest concentrations
amines showed the least relative change.
eptions to the general findings are
ed and it is suggested that separate
surements of free and bound amines may
ar up the discrepancies.

address)

Wollemann, M. Metabolism and bio-
mical action of phenothiazines. Revue
essologie, 1963, 4, 605-610.

experimental study was conducted to
ify Laborit's hypothesis that pheno-
azines act through the formation of
e radicals that would oxidize $HADPH_2$.
was observed that the chlorpromazine
e radical structure obtained by irrad-
ion can be converted into the initial
pounds by $NADH_2$ or $NADPH_2$. If the
adiated compound is given intravenously
rabbits, the characteristic phenothia-
e effect is observed earlier on the
than after injection of plain chlor-
omazine. In vivo phenothiazine oxi-
ion was studied in animal and in man.
one clinical investigation, determin-
ion of phenothiazine concentrations were
e from blood, CSF, and brain at various
ervals after i.v. and i.m. phenothia-
e administration. The author suggests
rther investigation in light of the
cumulation of findings which support the
e of phenothiazine as electron acceptors
the organism.

stitute of Neurosurgery
dapest, Hungary

530 Lehmann, A.,& Busnel, R.G. Metabolism of cerebral serotonin in its relation to the audiogenic crisis in mice and its variation under the influence of various psychotropic compounds. In Centre National de la Recherche Scientifique. Psychophysiologie, neuropharmacologie et biochemie de la crise audiogene. (Psychophysiology, neuropharmacology, and biochemistry of the audiogenic seizure.) Paris: Centre National de la Recherche Scientifique, 1963.

This study investigated whether the modification of brain level serotonin was related to the phenomenon of audiogenic seizure in mice. The serotonin was measured by spectrophotofluorometric recording method. It appeared that the audiogenic convulsions did not change the level of brain serotonin. A decrease in the serotonin level produced by reserpine increased the intensity of the convulsion and the incidents of death in seizure. An increase of the serotonin level produced by injections of serotonin, MAOI, or 5-hydroxytryptophan decreased the intensity of the convulsions or protected the mice from seizures. This same result was obtained by reversing the reserpine action when reserpine and MAO inhibitors were injected together.

(No address)

531 Smith, Robert L., Maickel, Roger P., & Brodie, Bernard B. ACTH-hypersecretion induced by phenothiazine tranquilizers. Journal of Pharmacology, 1963, 139, 185-190.

Sedative doses (5-20 mg/kg) of chlorpromazine and other phenothiazine agents are found to evoke a persistent hypersecretion of ACTH as measured by decreased levels of adrenal ascorbic acid, elevated levels of plasma corticosterone, and increased liver TPO (Trytophan Activity Pyrrolase). With the use of unanesthetized male Sprague-Dawley rats, the effects of the hydrochlorides of chlorpromazine, promazine, trifluoperazine,

and chlorpromazine sulfoxide on ACTH hypersecretion were investigated and found to cause an increase in adrenocortical activity as measured by depletions of adrenal ascorbic acid, rise in plasma corticosterone, increase in liver (TPO). The fact that none of the indices of adrenocortical hyperactivity were affected upon administration of chlorpromazine (5-20 mg/kg) to hypophysectomized or adrenalectomized animals indicate that the increased activity of the adrenal cortex in normal specimens had resulted from ACTH hypersecretion. Repeated doses of chlorpromazine are found to have a depressant effect on pituitary ACTH content. In this case, secretion has presumably outstripped synthesis. Similar depletion of ACTH is produced by prolonged exposure to cold or by large doses or reserpine. These studies obviously indicate that sustained hypersecretion of ACTH seems to be a part of the pharmacological syndrome of the phenothiazine tranquilizers. (20 Refs.)

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532 Dvornik, D., Kraml, M., Dubuc, J., Tom, Helen, & Zsoter, T. The effect of some inhibitors of the postganglionic sympathetic mechanism on monoamine oxidase. Biochemical Pharmacology, 1963, 12, 229-240.

In studying the effect of a series of inhibitors of postganglionic sympathetic transmission on liver monoamine oxidase, it was found that with kynuramine as substrate, they inhibited liver monoamine oxidase of rats, guinea pigs, and cats. The agents tested in vitro and some in vivo are chemically derivatives of benzyl-substituted quaternary ammonium and guandinium as well as β-phenoxyethyl-substituted guandinium salts. In both the quaternary ammonium and guanidinium series, orthosubstituents appeared to enhance the inhibition of monoamine oxidase in vitro and adrenergic transmission in vivo. Methylation of the guanidine portion, while enhancing the blocking effect on the nictitating membrane and increasing the toxicity, did not seem to affect the ability of the compounds to inhibit monoamine oxidase. In vivo, typic representatives were found to be relativel well-absorbed, peripherally acting inhibitors of monoamine oxidase. The author suggest that guanidinium analogs of bretylium, in addition to their adrenergic blocking properties, may also inhibit the monoamine oxidase in peripheral sympatheti fiber. (42 Refs.)

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533 Kirberger, E. Variable action of monoamine oxidase-inhibiting hydrazines on serotonin metabolism. Nature, 1963, 197, 1211-1212.

Only Marslid and Marplan of the MAO inhibiting hydrazines influence 5-hydroxyindoly lacetic acid (5-HIAA) excretion after loading with serotonin or 5-HIAA in the same way. Niamid and Nardil reduce the 5-HIAA excretion only after loading with serotoni The author rejects the conclusions of earlier investigators that MAO inhibiting hydrazines have a similar and practically synchronous effect on 5-HIAA excretion aft loading with serotonin and 5-HIAA. He doe not believe that this effect is caused by the same mechanism of action and that the action of these hydrazines on the serotoni loading test cannot be a result of the inhibition of MAO. The author interprets the action of Marslid and Marplan on 5-HIA excretion after loading with 5-HIAA as a side effect of these two substances.

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534 Guttman, Helene N., & Friedman, W. Evaluation of phenothiazines as membrane permeability alterants. Federation Proceedings, 1963, 22, 569. (Abstract)

sing methods which were previously devel-
ped for evaluating compounds which alter
otility and membrane permeability of Tetra-
mena pyriformis, we have tested several
henothiazine-tranquilizers for both prop-
rties. Evaluation depends upon comparison
f dose of phenothiazine required for T.
yriformis immobilization when the compound
s offered alone or in combination with a
econd agent which only enters in lethal
uantities when membrane permeability is
ltered. Immobilization efficacy by single-
ffered phenothiazines correlates with
linical effectiveness. They follow in
rder of decreasing immobilization ability:
rifluoperazine (TFP), prochlorperazine
PCP), perphenazine, fluophenazine (FP),
hioridazine, trifluopromazine, chlor-
romazine (CPZ), acetophenozine (AP), pro-
azine, and promethazine (PM). Grouping
ccording to ability to alter membrane
ermeability does not correlate with clin-
cal effectiveness. Ability to alter perme-
bility is expressed by amount (μM), to
mmobilize cells/ amount (μM), in presence
f second agent. This comparison indicates
ermeability alteration independent of
otency. TFP and CPZ are most active; FP,
M, AP, and PCP rank next. Inactivity of
PZ-sulfoxide emphasizes requirement for a
tructure which allows easy conversion to
free radical.

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ew York 17, New York

35 Shapovalov, A.I. Fiziologiya i
armakologiya sinapticheskoy peredachi voz-
uzhdeniya. (Physiology and pharmacology
f synaptic transmission of excitation.)
n: Val'dman, A. V. (Ed.), Aktual'nyye
roblemy farmakologii retikulyarnoy forma-
sii i sinapticheskoy peredachi, Leningrad:
Leningradskiy Meditsinskiy Institut imeni
kademika I. P Pavlova, 1963, Pp. 321-342.

The mechanism of synaptic transmission is
f primary importance in analyzing the
asic nervous functions and effect of var-
ous neurotropic compounds. Excitation is transmitted from cell to cell either by means of electrical stimulation or mediators, which either stimulate or inhibit the activity of the membrane of a postsynaptic cell. The following factors, affecting the basic stages of synaptic transmission, were studied: 1) activity of presynaptic endings and release of mediators; 2) onset and course of postsynaptic potentials; and 3) onset of a potential action in postsynaptic cells. Different pharmacological agents either stimulate or block chemoreceptors of a subsynaptic membrane. Ether, urethan, hexanal, and Nembutal inhibit the activity of postsynaptic membrane of nerve cells. Procaine and atropine inhibit the potentials of the activity of spinal neurons with synaptic, antidremic, and direct stimulation. Strychnine and caffeine increased the excitability of spinal neurons with direct stimulation. However, the method of iontophoretic micro-application is inadequate and therefore, new, more precise methods for studying the effect of drugs on cells and synapses should be elaborated.

(No address)

536 Arushanyan, E. B. O presinapticheskoy prirode tsentral'nogo tormozheniya. (The presynaptic nature of central inhibition.) In Val'dman, A. V. (Ed.) Aktual'formatsii i sinapticheskoy peredachi, Leningrad, I Leningradskiy Meditsinskiy Institut imeni Akademika I. P. Pavlova, 1963. Pp. 342-354.

The nature of the effect of different neurotropic drugs often depends completely on their ability of changing the course of elementary nerve processes (excitation and inhibition) in definite cellular elements of the central and peripheral nervous system. The function of nerve cells is inhibited either by an interaction of opposite effects (postsynaptic inhibition) or by an interaction of two flows of excitatory impulses in primary afferent tissues (presynaptic inhibition). In experiments

on gigantic synapses of stellate ganglions in crabs, the excitatory postsynaptic potential was completely inhibited when a value of presynaptic impulse was reduced by 80 percent. Experimental results established in invertebrates were confirmed by experimental results in warm-blooded animals. Different analgesics, even in large doses, had no effect on the polarization of spinal cells. Barbiturates in doses, which completely eliminated the discharges in postsynaptic cells, had no effect on the excitability of terminals of primary afferent neurons.

(No address)

537 Shevchenko, A. I. K farmakologii gladkikh myshts. (The pharmacology of smooth muscles.) In: Val'dman, A. V. (Ed.), Aktual'nyye problemy farmakologii retikulyarnoy formatsii i sinapticheskoy peredachi, Leningrad, I Leningradskiy Meditsinskiy Institut imeni Akademika I. P. Pavlova, 1963, Pp. 355-372.

The effect of nerve impulses on smooth muscles is associated, as in skeletal muscles, with the excretion of mediators such as acetylcholine, adrenaline, noradrenaline, and dopamine. The increased tonus of smooth muscles evoked by acetylcholine, physostigmine, pylocarpine, and choline is accompanied by the depolarization of cellular membranes, increased peak frequency, and high potentials. The hyperpolarizing effect of adrenaline results from increased concentration of potassium ions in cells. The problem of why adrenaline in one instance stimulates the contraction of smooth muscles, while in another evokes their relaxation remained unsolved. One of the most characteristic features of mypotropic drugs is that they eliminate spasms in smooth muscles evoked by different factors. The stimulating effect of histamine on smooth muscles is associated with the depolarization of fibers in smooth muscles. The effect of serotonin on bioelectrical activity of the fibers of smooth muscles is an important factor in the stimulating effect of the drug on smooth muscles. The stimulating effect of preparation P is also associated with the depolarization of muscular fibers The effect of analgesics on smooth muscles has not been studied adequately. In unnarcotized dogs, morphine considerably increased the tonus of small intestines, whereas in guinea pigs it had a pronounced effect on large intestines.

(No address)

538 Ballantine, E. The effect of gamma-aminobutyric acid on the audiogenic seizure In Centre National de la Recherche Scientifique. Psychophysiologie, neuropharmacologie et biochimie de la crise audiogene. (Psychophysiology, neuropharmacology, and biochemistry of the audiogenic seizure.) Paris: Centre National de la Recherche Scientifique, 1963.

A method for introducing GABA to the CNS was found in the direct placing of GABA on the cerebral cortex. It was found that GABA inhibited the audiogenic seiure in mice, giving various degrees of protection. This indicated that GABA may diffuse into th neuronal components while it has been shown that it will not pass the blood brain barrier. Controls, not treated with GABA, generally experienced the audiogenic seiure It was shown that the operations do not have any severe effect on the later behavio of the mouse.

(No address)

539 Van Praag, H. M., & Leijnse, B. Die Bedeutung der Monoaminoxydasehemmung als antidepressives Prinzip. II. (The significance of monoaminoxydase inhibition as an antidepressant principle, II.) Psychopharmacologia, 1963, 4, 91-102.

This study results in the conclusion that the revitalizing effect of the two tested antidepressive hydrazines, isocarboxazid and iproniazid, is not related to their MAO-inhibiting capacity, but to poor absorption

the gastro intestinal tract. The effect the two MAO inhibiting hydrazines on metabolism of exogenous serotonin was died in 18 depressed patients. The trol group consisted of 14 healthy male female subjects. Serotonin (5-HT) was inistered weekly for 2 weeks before and 6 weeks during treatment with the razines. Nine subjects received ipron-id (100 mg daily) and nine subjects carboxid (40 mg daily). Four patients did not react to the drugs were given ctroshock. Seven patients were given ernately serotonin and 5-HIAA 1 to 2 es per week. The two hydrazines were nd to reduce the production of 5-HIAA er oral administration of 5-HT. This nomenon was not correlated with the elopment of physical changes, nor did seem to be brought out by MAO activity ckage. Electroshock therapy had no luence on the exogenous 5-HT metabolism. 6 out of 7 patients with agitated de-ssions, the 5-HIAA production was ab-mally low after administration of 5-HT, IAA, respectively. The quantities reased as the agitation subsided, ir-pective of therapy. (14 Refs.)

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terdam, Holland

) Bozzi, R., De Maio, D., & Calvi, N. ncefalometria isotopica. Nota II. Il maencefalogramma con sieralbumina umana ^{1} in un gruppo di schizofrenici cronici. otopic encephalometry. Note II. The ma-encephalogram with human serum albu-labeled with I^{131} in a group of chronic izophrenics.) Acta Neurologica, 1963, 583-625.

sical changes in the brain of 40 chronic izophrenics (28 males and 12 females), to 63 years old, and hospitalized for 2 years, were studied by means of the ma-encephalogram. Of the patients 12.5% e within the limits of normality, 37.5% were flat more or less with a slight asymmetry, and 50% were more or less distinctly asymmetric with diffuse or focalized hypogamma emission in two or more leads. Pneumoencephalography was used for comparative study. In 4 out of 5 patients, there was normal gamma-encephalogram compared to pneumoencephalogram finding. In 12 of 14 cases, a flat gamma-encephalogram, more or less uniform, coincided with pneumoencephalogram finding. In 10 out of 20 cases, there was a clear superimposition between the zones of hypogamma emission and monoventricular dilation.

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541 Fotherby, K., Ashcroft, G., Affleck, J. W., & Forrest, A. D. Studies on sodium transfer and 5-hydroxyindoles in depressive illness. Journal of Neurology and Neurosurgery and Psychiatry, 1963, 26, 71-73.

The rate of transfer of ^{24}Na from blood to cerebrospinal fluid was compared in groups of patients with depressive illness and schizophrenia. There was no significant difference between these two groups in the rate of ^{24}Na transfer. However, the transfer rate in a small group of severely depressives (without paranoid symptoms) was lower than the whole group of depressives. Exercise appeared to increase the transfer rates which may have been due to more rapid mixing of ventricular fluid with cerebrospinal fluid. There was no significant difference between the two groups in the levels of 5-hydroxyindoles in blood or cerebrospinal fluid. The levels of 5-hydroxyindoles in cerebrospinal fluid tended to rise after exercise.

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542 Forrest, Fred M., Forrest, Irene S., & Roizin, L. Clinical, biochemical and post mortem studies on a patient treated with chlorpromazine. Revue Agressologie, 1963, 4, 259-265.

The authors present a clinical, biochemical, and histopathological, and neuropathological study of a 39-year-old patient who died of coronary occulsion after prolonged treatment with phenothiazine derivatives. Since the number of mental patients who improve only after prolonged and continuous phenothiazine treatments is increasing, a coordinated chemical and pathological study was carried out. The patient had undergone insulin treatment and bilateral lobotomy in the course of his chronic disease, so that the changes in the neuronal and visceral structures and in the neuronophagy of the extrapyramidal nuclei, and the depigmentation of the neurons and of the substantia nigia cannot be clearly attributed to neuroleptics. The distribution of chlorpromazine in the tissues does not differ much from what is seen in laboratory test animals. The lung tissue and all the glandular structures of the patient contained a much greater accumulation of the drug than was to be found in the various brain tissues. The bone tissues and lipids did not contain any chlorpromazine, while the hair showed a maximum accumulation. Methods of determining drug contents, especially in the lipids and nails, are being improved.

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Palo Alto, California

543 Gothelf, Bernard, & Karczmar, Alexander G. Quantitative colorimetric method and extraction procedure for determination of chlorpromazine in animal tissues. International Journal of Neuropharmacology, 1963, 2, 95-99.

A procedure for quantitative analysis of chlorpromazine from biologic tissues based on oxidation of CPZ by ferric ion in the presence of concentrated sulfuric acid, and on its extraction into alkaline ether, is described. Cherry-red chromophore is read spectrophotometrically. Eighty to 90 percent recoveries, after its incubation with brain homogenates, could be obtained by this method. The procedure was specifi for chlorpromazine and other 2-chloropheno thiazines possessing a side chain on the ring nitrogen; color was not present, or a different color was obtained, with chang in the phenothiazine nucleus and with substitutions for chlorine in the presence of ferric ion. (Author summary)

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544 Mueller, Peter S., & Evans, Warren H Responses of plasma glycerol concentrations to epinephrine, norepinephrine, glucose, insulin, and prolonged fasting in man. Journal of Laboratory and Clinical Medicine, 1963, 61, 953-961.

Plasma glycerol and FFA (free fatty acid) concentrations were measured in volunteers before and after saline, epinephrine, norepinephrine, glucose, and insulin infusions and during a 24 hour fast. The mean concentration of glycerol after an overnight fast was 0.082, S.E. ± 0.025 mu M per milliliter. There was no correlation between glycerol and FFA concentration at this time Infusions of saline produced no significant change in glycerol or FFA concentrantion. Significant elevations of glycerol and FFA were noted after epinephrine and norepineph rine. After the infusion of these catecholamines the plasma glycerol and FFA had signficant positive correlations. After 24 hours of fasting there was a significant rise in plasma glycerol but this elevation occurred 6 hours later than the increase in FFA. There was no correlation between FFA and glycerol concentrations at any period of the fast. After insulin and glucose there were significant falls in plasma glycerol and FFA. The ratio of FFA to glyce

ll sharply at this point. After sulin there was a significant negative rrelation between FFA and glycerol con- ntration in the plasma. The rise in asma FFA, 2 to 4 hours after intravenous ucose, was not accompanied by signif- ant increases in plasma glycerol. The sitive correlation of FFA with glycerol s highly significant at this time, similar the observations after epinephrine, nor- inephrine infusions.

tional Institute of Mental Health
thesda, Maryland.

5 Gornicki, B., Bozkowa, K., Kurzepa, ., Cabalska, B., Rutkowska, A., & roszewicz, A. Studies on brain tissue d mitochondrial respiration and the action MAO inhibitors in the course of onto- netic development. Bulletin of Polish dical Science and History, 1963, 6, 21-23.

e respiration of brain tissue and of iso- ted mitochondria in ontogenetic develop- nt, as well as the action of phenelzine ardil) on this enzyme, was studied in ts (1 to 90 days old) and rabbits (1 day 6 months of age). Mitochondria of the ain were obtained by fractional centri- gation. Tissue respiration was deter- ned by the Warburg method. Studies on ssue respiration showed that there are fferences in the amount of oxygen con- med, depending on age. Thisincreases the spiration of the whole brain tissue as ll as of the mitochondria. The greatest hibitory action of phenelzine was found 1-day-old animals: Until the 12th day life the influence of phenelzine dimin- shes. Stabilization of inhibitory action ccurs from this point to maturity.

esearch Institute of Mother and Child
arsaw, Poland

46 Hopkins, Thomas F., & Pincus, Gregory. nti-ovulatory effects of reserpine when dministered to immature rats. Federation roceedings, 1963, 22, 506. (Abstract)

Antiovulatory effects of reserpine were tested in intact and in hypophysectomized immature rats treated with exogenous gonadotropins. Follicular development was produced by administering pregnant mares serum (PMS) and superovulation was induced by treatment with human chrionic gonadotropin (HCG). A single injection of reserpine given approximately 1 minute before (HCG) was effective in suppressing ovulation in hypophysectomized rats. When given at various other times before HCG, ovulation was not inhibited although the animals may have been under the tranquilizing effects of reserpine at the time of autopsy. Reserpine was essentially ineffective when given to intact rats at the time of HCG treatment. When given at an earlier time, ovulation could be reduced to about one-half that of the controls. Thus our data show that induced superovulation in the hypophysectomized immature rat may be suppressed by a single injection of reserpine, and that the antiovulatory effects are probably not directly related to the tranquilizing activity. They suggest also an interference with the ovulation-inducing activity of HCG on the ovarian follicle. (Author abstract).

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Shrewsbury, Massachusetts

547 Goldstein, M., Musacchio, J., & Gerber, H. Metabolites of DOPA and dopamine in the rat brain. Federation Proceedings, 1963, 22, 389. (Abstract)

Dopamine-C^{14} was given to rats i.p. and 1 hour later the animals were sacrificed. By ion exchange and paper chromatography, the metabolites of DOPA and dopamine were isolated. When DOPA-C^{14} was administered to the animals, DOPA, dopamine, norepinephrine, 3-O-methoxyamines as well as 3,4-dihydroxy-phenylacetic acid, 3-methoxy-4-hydroxy-phenylacetic acid, 3, 4-dihydroxy-phenylethanol (MHPE) were isolated from the brain. When dopamine-C^{14} was administered, only the phenolic alcohols DHPE and MHPE were found in the CNS. This

demonstrates that DHPE and MHPE accumulate in the brain through uptake from the blood. Based on the analysis of MHPE in the blood and CNS after administration of DOPA, and dopamine, phenolic alcohols are formed in the CNS itself. (Author abstract)

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548 Guth, P. S., Sellinger, O. Z., Amaro, J., & Elmer, L. Additional permeability effects by chlorpromazine "leakage" of lysosomal phosphatase. Federation Proceedings, 1963, 22, 626. (Abstract)

Chlorpromazine has previously been shown to affect the permeability of mitochondria, red blood cells, pinched-off nerve endings, and other membranes. Since a general membrane action was proposed as the explanation of its wide variety of effects, it seemed necessary to include the lysosomal membranes in the group of membranes studied. The "leakage" of lysosomal acid phosphatase was selected as the parameter of membrane function to be investigated. The rat liver "light" mitochondrial fraction known to contain lysosomes was isolated in 0.6 M sucrose and was incubated at 37° C, pH 5.0 in 0.6 M sucrose for 1 hour before assay. This procedure causes 35%-50% of the total phosphatase activity to appear in the supernatant (9.6×10^8 gravities-minute). Chlorpromazine in doses less than 5×10^{-4} M produces up to 50% inhibition of the enzymic "leakage." Higher concentrations produce an increase in "free" activity. This biphasic effect is consistent with chlorpromazine effects in other systems, e.g., mitochondria. It seems likely that a constituent common to many types of membranes interacts with chlorpromazine. (Author abstract)

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549 Giarman, Nicholas J., & Pepeu, Gianc lo. Relationship of brain acetylcholine and certain anticholinergic psychotomimeti and amnesic compounds. Federation Proceedings, 1963, 22, 215. (Abstract)

Large doses of atropine and scopolamine produce a significant fall in whole brain levels of total acetylcholine (ACh) in the rat. This effect on brain ACh has been elicited by as little as 0.63 mg scopolami /kg and 5.0 mg atropine/kg. With scopolamine, the effect is most pronounced in 30 minutes and disappears in 120 minutes. Almost all of the decline in brain ACh after both scopolamine and atropine can be accounted for by the change in ACh levels in the cerebrum; negligible changes were observed in the brain stem. With a series of synthetic anticholinergic agents, the reduction in brain ACh was found to be related to psychotomimetic potency; no change was seen after the administration of a compound with only peripheral anticholinergic activity or one with central anticholinergic activity, but without psychotomimetic action. The mechanism of this effect may be related to central ACh release. (Author abstract)

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New Haven, Connecticut

550 Laborit, H., Brue, F., & Leterrier, F. Sur le mécanisme inhibiteur de l' adrénaline sur l'iléon isolé et l'oreillette isoleé du lapin. (On the inhibitive mechanism of adrenaline on the isolated ileum and auricle of the rabbit.) Revue Agressologie, 1963, 4, 443-447.

On the isolated ileum and auricle of the rabbit, the authors show that the iproniazid, MAO inhibitor, is not an antagonist for the action of the epinephrine. So, it does not seem that the action of the epinephrine may be attributed to the oxydation of neuroamines into aldehydes; thes aldehydes being secondarly reduced into

cohols by the hydrogen of the NADP, the ydation of which trains, finally, the G6P, the hexose monophosphate shunt. This chanism has been lately proposed to ex- ain the glucose oxydation, in the pentose thway, under the action of the neuroamines, the anterior hypophysis. In all these ses, the authors think that such an orien- tion results from the metabolic structure self of the studied organs, that they put the before defined group A (pentoses+). uthor summary)

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pital Boucicaut
ris XV, France

1 De Maio, D., & Pasquariello, G. Gamma- ino-beta-hydroxybutyric acid (GABOB) and ain serotonin. Psychopharmacologia, 1963, 84-86.

mma-amino-beta-hydroxybutyric acid (GABOB) jected intraperitoneally in cats at the se of 0.5g/kg cause a significant decrease brain serotonin. Twenty-five cats were vided into 5 equal groups; one group re- ived a placebo. The brains were weighed ter decapitation (2, 8, 24, & 48 hours ter the injections) and the brain sero- nin was extracted. Statistical evaluation the results was done by analysis of riance and comparison of the separate erages. The reduction of brain serotonin s still present after 24 hours and dis- pears after 48 hours of injecting GABOB.

tituto Ospitaliero Provenciale
lano-Affori, Italy

2 Magee, W. L., & Rossiter, R. J. In- rporation of inorganic P^{32} into phospho- pids of brain slices. Effect of certain anquilizing drugs. Canadian Journal of ochemistry and Physiology, 1963, 41, 55-1162.

ese studies reveal that the incorporation inorganic P^{32} into the phospholipids slices of guinea pig brain is stimulated by the following phenothiazine derivatives: promazine, promethazine, tetrameprozine, and WY1172. Promethazine, as well as chlor- promazine, at a concentration of 0.1 mu M produced a maximum increase in phospolipid labeling. It did not stimulate respiration and aerobic glycolysis, nor did it increase the phosphocreatine in the slices. The authors consider it important that methylene blue, a phenothiazine derivative with no known tranquilizing effects, did not stim- ulate the labeling of phospholipid, while pipradol and mepazine as well as azacyclonal had this stimulating action. Meprobamate and phenaglycodol, which also had no label- ing effect, have a predominantly peripheral action, while phenothiazine derivatives and piperidine act on the higher centers of the nervous system.

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553 Schaeppi, Ulrich. Comparison of sero- tonin with directly and indirectly acting compounds in their effect on the nictitat- ing membrane of spinal cats. Journal of Pharmacology and Experimental Therapeutics, 1963, 139, 330-336.

Studies on the action of serotonin and some related compounds on the chronically and acutely denervated nictitating membrane of spinal cats revealed that serotonin, nor- epinephrine and acetylcholine activate its muscle and acetylcholine activate its muscle at different receptor sites. On acutely denervated preparations previous serotonin injections potentiated the effect of sub- sequent injections of the three agents. Tyramine, nicotine, and tryptamine, the three indirectly acting agents, were also studied for the production of contractions of the nictitating membrane. Tryptamine was only one-twentieth as effective as norepinephrine. All injections were given via the carotid artery.

Worcester Foundation for Experimental Biology
Shrewsbury, Massachusetts.

554 Cochin, Joseph, & Daly, John W. The use of thin-layer chromatography for the analysis of drugs. Isolation and identification of barbiturates and nonbarbiturate hypnotics from urine, blood and tissues. Journal of Pharmacology, 1963, 137, 154-159.

A methodology is described for adaptation of thin-layer chromatography to isolation and identification of barbiturates and nonbarbiturate hypnotics. The hypnotics are extracted from tissue homogenate, urine, or blood into methylene chloride at pH 5.0. The extracting solvent is evaporated and the drugs are spotted on thin-layer chromatoplates after having been taken up in ethanol. The usefulness of thin-layer chromatography in metabolic studies as well as in toxicology and forensic medicine is stressed. It is also noted that a heretofore unisolated metabolite of secobarbital was isolated from human urine by this method.

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555 Schwartz, D. E., Burkard, W. P., Roth, M., Gey, K. F., & Pletscher, A. Effect of chlorpromazine on the penetration of monoamine oxidase inhibitors and monoamine releasers into rat brain. Archives Internationales de Pharmacodynamie, et de Therapie, 1963, 14, 135-144.

Chlorpromazine seems to interfere with the permeation of monoamines or their precursors through brain membranes and not by absorption of MAO inhibitors or releasers or the penetration of these drugs into the brain. Rats, of both sexes, were pretreated with 20 mg/kg chlorpromazine i.p. before administration of benzylhydrazine, isocarboxazid, iproniazid, reserpine or the benzoquinolizine derivative Ro 4-1284. After decapitation the brain and blood plasma were checked for drug concentration and MAO inhibition. It was found that the chlorpromazine pretreatment of rats counteracted the increase of monoamine content in the brain, due to MAO inhibitors and the decrease caused by MA releasers. The brai blood ratio of benzylhydrazine was not significantly modified, nor was MAO inhi ition, induced by benzylhydrazine, isocar azid, and iproniazid, influenced by chlorp mazine.

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Basle, Switzerland

556 Schmidt, J. L., & Fleming, W. W. structure of sympathomimetics as related reserpine induced sensitivity changes in the rat ileum. Journal of Pharmacology, 1963, 139, 230-237.

The magnitude of the increase or decreas in sensitivity to sympathomimetic drugs the rabbit ileum following reserpine pre treatment is dependent upon their chemic structure. These drugs may have both direct and indirect action and differ on in the ratio of direct to indirect acti The "para" and "meta" hydroxyl groups are not both essential to direct action. Di action is only slightly reduced by the di chloro substitution for the hydroxyl gro on the catechol nucleus. While the beta hydroxyl group is important for direct ac tion, the substitution of a meta methoxy a meta hydroxyl group reduces the direct action. It has been found though that th meta methoxy group produces greater direc action, than if no meta substitution is made at all.

Department of Pharmacology
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557 Schanberg, Saul, M. A study of the transport of 5-hydroxytryptophan and 5-hydroxytryptamine (serotonin) into brain. Journal of Pharmacology, 1963, 139, 191-2

The uptake of 5-HT-1-C^{14} and DL-5-HTP-1-C its precursor, by rat brain slices was st ied to understand both the synthesis of 5

the availability of 5-HT to the brain. TP transport was facilitated by enhance- t of the slice/medium concentration ratio O_2 and glucose, by interference with this ancement by dinitrophenol, and by pro- ing optimal concentrating conditions. er similar conditions 5-HT transport was facilitated. 5-HTP transport was not ilitated by such drugs as phenobarbital, phine, reserpine, chlorpromazine, LSD-25, pramine, and iproniazid although these gs depress respiration of brain tissue influence the metabolism of 5-HT. The urally occurring amino acids, L-trypto- n, L-phenylalanine, L-tyrosine, L-di- roxyphenylalanine, L-leucine, L-iso- cine, and L-proline cause a decrease in 5-HTP uptake by brain slices.

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Fumagalli, Remo, Grossi, Enrica, & letti, Pietro. The effect of imipramine Desmethylimipramine on lipid biosynthesis brain and liver. Journal of Neuro- emistry 1963, 10, 213-217.

dies on the effect of imipramine and des- hylimipramine on brain and liver lipid thesis in rats in vivo experiments showed at desmethylimipramine stimulates brain utral fat and phospholipid fatty acid syn- esis. In in vitro studies both drugs in- eased neutral fat fatty acid synthesis the brain at high concentrations of 10^{-3}M. They decreased acetate oxidation d cholesterol synthesis at the high concen- ation, while at a lower concentration of 10^{-4}M phospholipid fatty acid synthesis s increased. The drugs seemed to have no fect on liver lipid synthesis or on P^{32} corporation into brain lipids.

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Pavlin, Rudi. The effect of lysergic id diethylamide on the acetylcholinesterase tivity of single nerve cells from the re- cular formation. Journal of Neurochem- try, 1963, 10, 195-199.

The acetylcholinesterase activity of single nerve cells of the reticular formation of the rat brain was found to be inhibited 2×10^{-5}M and activated at lower concentrations. Albino rats, both male and female, were decapitated, the brain was removed and a 1-2 mm thick section of the desired area was placed in sucrose solution. The cells were stained with methylene blue and sucked into an ampulla microdiver. The acetylcholinesterase activity of two uninhibited cells was compared with that of two cells to which LSD was added. CO_2 production was calculated and cell volume assessed. The results obtained were in good agreement with previously established electrophysiological data. It is not clear whether the electrophysiological observations were due to acetylcholinesterase inhibition or activation.

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560 Wise, B. L., Van Brunt, E. E., & Ganong, W. F. Effect of removal of various parts of the brain on ACTH secretion in dogs. Proceedings of the Society for Experimental Biology and Medicine, 1963, 112, 792-795.

Adrenocortical response to trauma of cannulating the adrenal vein has been tested in mongrel dogs 4 hours before the removal of various parts of the brain. Compared to controls, 17-hydroxycorticoid output in adrenal venous blood is slightly decreased in dogs in which all brain tissue above the pons (except the hypothalamus) has been removed. Output was lower, but above basal levels in dogs in which the entire brain above the pons had been removed. The range was the same when the entire brain was removed. Acute section of the pituitary stalk decreased the adrenocortical response to an approximately equal degree. Removal of the pituitary, as well as the brain, reduced output to low levels. These data do not support the hypothesis

that the hindbrain secretes a factor which stimulates the pituitary to secrete ACTH. Other explanations are discussed.

University of California School of Medicine
San Francisco, California

561 Leau, O. Relation entre concentration sanquine et activite therapeutique. (Relationship of blood concentration and therapeutic action.) La Presse Medicale, 1963, 42, 1969-1972.

Numerous experimental studies on various drug groups, including those affecting the central nervous system, have shown that a drug can be very active even if it is found in the blood in only the smallest quantities or if it has disappeared from the blood. It seems that the therapeutic activity is inversely proportional to its concentration in the blood. The authors suggest that a drug should not be considered ineffective because no traces can be found in either the blood or the urine.

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Pollitt, John. **The current status of the tranquillizers.** Current Therapeutics, 191:530-538, 1963.

nquilizers may be divided into major and or groups. The major tranquilizers include the penothiazines, the Rauwolfia alkaids, haloperidol, and lithium carbonate. ir chief use is for reduction and abolin of psychotic symptoms and resulting avior disturbances. Two well-known minor nquilizers are chlordiazepoxide and meamate. These drugs are useful in treatt of patients with acute anxiety states, pical depression, and premenstrual tenn.

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Frommer, Eva. **Physical treatments in psychiatric nursing---4. The use of ulin.** Nursing Times, 59:300-302, 1963.

ulin in subcoma doses speeds metabolism, ducing general improvement and a consent receding of neurotic disabilities. It useful par excellence in the treatment of rexia nervosa. The phenothiazines have ved more useful, more easily administered, possibly more specific than coma treatt of schizophrenics, now reserved only cases in which it is the only means of endering a therapeutic response. In some izophrenics, only two or three sopors are ded to initiate improvement, and insulin then reduced to a very small dosage. In ients not responding to high dose of inin, the administration of 600 units one and 60 units the next day often produces matic response. Patients with degenerae heart disease, those 60 years of age, those with endocrine disorders are untable for modified insulin treatment.

address)

Prange, Arthur J., Jr., Cochrane, Carl M. & Abse, D. W. **Changing psychiatric atment patterns and their relationship to ouble blind tranquilizer study in a teach- hospital.** Journal of New Drugs, 3:75-84, 3.

A double-blind study of the effects of tranquilizers on acutely disturbed mental inpatients was conducted from 1955 to 1961 on 3,206 patients between the ages of 18 and 59, who showed sufficient agitation, anxiety, or stress to indicate daytime sedation. Initial test substances were reserpine, powdered opium, and lactose. Chlorpromazine was added in 1959, and a proprietary composed of 0.3 mg ergotamine tartrate, 0.1 mg Bellafoline, and 20.0 mg phenobarbital replaced the opium in 1960. As part of the final evaluation of the study, changing psychiatric treatment patterns and their relationship to the double-blind study were assessed. Conclusions are that somatic treatment procedures in the hospital had remained strikingly constant, despite the "ambient revolution" in psychiatric treatment methods. Only 38% of the patients received physical treatment. It is noted that hospitals with different problems, goals, resources, and beliefs tend to employ different treatments, according to the need as they perceive it.

School of Medicine
University of North Carolina
Chapel Hill, North Carolina

565 Mark, Lester C. **Metabolism of barbiturates in man.** Clinical Pharmacology and Therapeutics, 4:504-530, 1963.

This review is concerned primarily with those aspects of metabolism of barbiturates that have been elucidated directly in man. An extensive discussion of the animal and human studies on the major sites of metabolis transformation, the liver, and the kidney is given. Mention is made of the other tissues that are involved to a lesser extent (brain, muscle, spleen, heart, intestines, and erythrocytes). There is often a scarcity of experimental data with man, and with the species differences in drug metabolism, the data cannot be interpolated directly without caution. The four pathways of barbiturate metabolism are described: (1) oxidation (to alcohols, ketones, or acids) of substituents in position 5 of the barbiturate ring; (2) loss of alkyl groups attached to a nitrogen atom; (3) desulfuration of thiobarbiturates; and (4) hydrolytic splitting of the barbiturate ring. Two additional pathways were

investigated: 5-dealkylation and N-methylation. The metabolic rate in man and findings from animal and human studies on induced acceleration of the rate are given. In conclusion, excluding only barbital, which is practically quantitatively excreted by the kidney, the major fraction of these drugs is metabolized in vivo, presumably by microsomal enzymes in the liver. Acceleration of the enzyme activity, amply documented in animals, may ultimately prove a significant factor in barbiturate metabolism in man.

Columbia University
New York, New York

566 Perk, David. **Psychotropic drugs—— their action and value.** South African Medical Journal, 37:194-197, 1963.

The neurophysiology has focused attention on the neurohumoral substances, such as serotonin, nor-epinephrine, and acetylcholine, and on the reticular system. The observations that serotonin antimetabolites, such as LSD and mescaline, are psychotogenic, and that drugs releasing or increasing brain serotonin favorably affect mental symptoms, indicate that the amount of serotonin in the brain may be related to the symptomatology of mental illness, for instance, in schizophrenia. Apart from its effect in breaking down serotonin freed at the synapses, it is possible that monamine oxidase may be implicated in the blood-brain barrier. The hypothalamus and parts of the reticular system are depressed by the weaker phenothiazines, whereas the more potent phenothiazines influence mainly the limbic system, particularly the amygdaloid and hippocampal segments. The former tend to induce autonomic-endocrine side effects and allergic reactions, whereas the latter tend to provoke seizures and extrapyramidal reactions. Familiarity with the side effects and toxic manifestations of psychotropic drugs is necessary to obviate adverse and deleterious reactions to them.

Tara Hospital
Johannesburg, South Africa

567 Glick, Burton S. **Inadequacies in the reporting of clinical drug research.** Psychiatric Quarterly, 37(2):234-244, 1963.

A group of 28 of 34 reports previously discussed, pertaining to chlorpromazine treatment of chronic, hospitalized schizophrenics, was evaluated from the point of view of thoroughness of the study, and of completeness of reporting, especially of the research design. Although some of the reports were quite adequate, the majority were lacking in some of the following categories: blindness (single or double-blind); controls (placebo or nonplacebo, both own control and separate-group control); chlorpromazine dosage; duration of chlorpromazine treatment; duration of hospitalization and illness; severity of illness and patient types; criteria of improvement; types of evaluating personnel; standard laboratory procedures; frequency of contact between patient and evaluators; extent of concurrent therapies; and consideration of side effects. Of the 28 papers, 15 were from the united states (14 state hospitals and 1 Veterans Administration hospital), 8 were from mental Hospitals in Great Britain, and 1 each was from Finland, Switzerland, Greece, Australia, and Norway.

New York University School of Medicine
New York 16, New York

568 Cahen, Raymond L. **Evaluation of the teratogenicity of drugs.** Clinical Pharmacology and Therapeutics, 5(4):480-514, 1963.

This review is divided into three parts. The first part consists of a complete investigation of the literature. The second part compares the various experimental conditions used in producing congenital malformations, outlines the procedures suggested in various countries, and evaluates the procedures used. The third part is a record of the author's personal experience in testing the teratogenic potentialities of new drugs.

Lafon Research Center
Maisons-Alfort, France

569 Benoit, J. C. **Les substances hallucinogenes. Leur role dans la recherche et dans la therapeutique psychiatriques actuelles. (Hallucinogenic agents. Their role in research and in current psychiatric therapy.)** Semaine des Hopitaux de Paris, 39(46):2148-2190, 1963.

Chemical isolation of numerous hallucinogenic substances, such as LSD 25, mescaline, and psilocybine (toxic mushrooms), has become important in psychiatric research, and these substances are being used as adjuncts

psychotherapy. Psychodysleptic intoxica-
ns exhibit a remarkable syndromal unity,
nly stimulating the diencephalic ergo-
pic zones. From the psychopharmacologi-
viewpoint, LSD 25 is important because
its powerful action on the CNS in minimum
es, its exact parallel between dosage and
ponse, and its implication in study of
mechanism of action. The difference in
tent of the psychiatric disturbances has
gnostic value. The disinhibiting effect
psychodysleptics in psychotherapy facili-
es abreaction and stimulates imagination,
le maintaining consciousness and memory.
traindications are antecedent acute psy-
tic episode, hysterical or pronounced
iety structure, psychopathic states with
ressiveness, and "useful" neuroses or neu-
es having secondary benefits that are too
ortant to the patient.

ital Psychiatrique de Villejuif
lejuif, France

DeGraff, Arthur C. & Lyon, Alan F. **Mebutamate. Antihypertensive or tranlizer?** American Heart Journal, 65:569, 3.

hough mebutamate is being promoted as a
d antihypertensive with central action,
dence shows that it is primarily a seda-
e or tranquilizer, and any effect on hy-
tension is due to sedation and not to
cific reduction of blood pressure. Drows-
ss was noted in every case when an anti-
ertensive effect was achieved with mebut-
te alone. Chemically a close relative of
robamate, it has greater sedative effect
n the latter in comparable doses. Mebut-
te is given in doses of 300 mg t.i.d. or
.d. Addiction of mebutamate did not in-
ease the antihypertensive effect of hydro-
lorothiazide.

) Park Avenue
York 21, New York

Ungar, Georges. **Excitation. (Part IV. Pathology and pharmacology of excitaon.)** Springfield, Ill., Charles C. Thomas, 3. 437 p. (American Lecture Series, No.).

rt IV, entitled "Pathology and Pharmacology
Excitation," of the book covers the fol-
ving: (1) Excitation, Injury and Disease:
flammation as Tissue Excitation---phlogo-
ic stimuli, signs of excitation in in-
mmation, capillary permeability, mast cells, and role of the nervous system; (2) Stress: Shock---mechanisms of shock and significance of Shock; (3) Excitation and Drug Action: Receptors or Pharmacoceptive Sides---general cytoplasmic poisons, enzymes as receptors, receptors and ions, and receptor proteins; (4) Drug Acting on Cellular Excitation---drugs acting on sensory receptors, drugs acting on effectors, and drugs acting on synaptic transmission; (5) Drugs Acting on the Central Nervous System---Excitants and central nervous depressants; and (6) Man and the Pharmacological Control of Information.

Institute for Comparative Biology
San Diego, California

572 Carlton, Peter L. **Cholinergic mechanisms in the control of behavior by the brain.** Psychological Review, 70:19-39, 1963.

The hypothesis that the tendency to respond is positively related to the level of activation of an animal, and is inversely related to the antagonistic cholinergic system, is supported indirectly by many other previous experiments. The reticular system, actuated by the catecholamines (epinephrine, norepinephrine, and dopamine) and acetylcholine, normally metabolized in the presence of cholinesterase and specifically blocked by anticholinergics, such as scopolamine and atropine, may interact to control several aspects of learned behavior. All drug experiments discussed used rats or mice, because the metabolic processes underlying the systems investigated differ markedly from species to species.

Squibb Institute for Medical Research
New Brunswick, New Jersey

573 Goldberg, Leon. **The predictive value of animal toxicity studies carried out on new drugs.** Journal of New Drugs, 3:7-11, 1963.

The factors of successful prediction of toxicity are these: (1) one must know how to look; (2) what to look for; and (3) one must look under the appropriate circumstances. The first is based mainly on experience; the second is based on clues from the chemical structure; and the third requires some knowledge of the pharmacodynamics and metabolism of the compound being tested. Radioisotope labeling combined with autoradiography offers a valuable, speedy, and economical

method. Tests of anticancer agents on mice, rats, and dogs had good predictive value for toxic effects on bone marrow, gastrointestinal tract, liver, and kidney; but the animal tests were less dependable in regard to nervous-system toxicity. In clinical studies, neither rodents, dogs, nor monkeys seem able to give warning of dermatitis and alopecia. A well-conducted 90-day test in two species, such as the rat and dog, provides a very high proportion of the basic facts likely to emerge from longer studies. The sensitivity of methods for detecting early changes and the specificity of tests for particular toxic effects are very important in improving safety tests of drugs.

The British Industrial
Biological Research Association
London, W.1, England

574 Kris, Else B. **Office treatment of the depressed.** Virginia Medical Monthly, 90:228-231, 1963.

Treatment of depression by a general practitioner is discussed from three aspects: (1) Can the various symptoms of depression be treated? (2) How can they be treated? (3) What risks are involved in such a therapeutic undertaking? Six types of depression that are most commonly encountered are described: reactive depression, manic-depressive psychosis, involutional psychosis, senile depressions, schizophrenic depressions, and post-partum psychosis. Depressions respond well to treatment, particularly when treatment is begun at an early stage. The general practitioner, however, must carefully evaluate each case to decide which patient can be treated on an ambulatory basis and which patients must be hospitalized because the danger of suicide is too great. Antidepressant drugs, such as iproniazid, imipramine, and tranylcypromine, are effective in controlling depression in ambulatory patients. Doses of 25 to 50 mg of imipramine, 3 to 4 times daily, control depressive symptoms in many cases within a few weeks, with few, if any, drug side effects. A complete regimen for treating an ambulatory patient with depression is described. Aside from the drug side effects, the greatest risk in treating depressions is the risk of suicide. Means for evaluating the degree of risk are described.

New York State Department of Mental Hygiene
New York, New York

575 Havens, Leston L. **Problems with the use of drugs in the psychotherapy of psychotic patients.** Psychiatry, 26:289-296, 1963.

Eight years of experience with drug therapy as a part of the long-term psychotherapy of psychotic inpatients and outpatients has resulted in a gradual change of approach to the use of drugs. The patient is now encouraged to participate in decisions regarding his drug therapy. Thus, he reports to the doctor his reactions and feelings regarding the drugs being taken, and these reactions are taken into account in subsequent decisions. To complete the relationship, the doctor should make information available to the patient in regard to the drug therapy, such as the purpose of the medication. Successful sharing of such responsibility, however, depends upon a correct appraisal of the patient's abilities, and waits, of course, upon the existence of some rapport between doctor and patient. In attitude toward drug therapy, patients can be divided into three categories: those who refuse it (generally paranoids), those who are noncommittal (usually catatonic), and those who request it (typically depressed or neurasthenic). The value to the psychotic patient of sharing the responsibility for his own treatment and management cannot be overemphasized. Chlorpromazine has been the drug most often used; one of its occasional side effects is production of lactation.

Massachusetts Mental Health Center
Boston 15, Massachusetts

576 Lewis, J. J. **Antidepressives and tranquillisers.** Pharmaceutical Journal, Summer Issue:85-91, 1963.

The following are reviewed and discussed: Tranquilizers---phenothiazines; phenothiazines used for other purposes (anti-Parkinson agents, antihistaminics, and anthelmintics), benzhydryl derivatives used as antihistaminics, antiemetics, and an anticholinergic; glycerol and butanediol derivatives; and muscle relaxants; Antidepressives---beta-phenylethylamine derivatives, hydrazine derivatives, benzhydryl derivatives, and others; Chemical Transmission; Acetylcholine; Reticular Formation of the Brain Stem; Noradrenaline and 5-hydroxtryptamine; Noradrenaline; 5-hydroxytryptamine; Gamma-aminobutyric acid; Biochemical Processes; Phosphate Metabolism; and Adenosinetriphosphatase.

(No address)

577 Lasky, Julian J. **The problem of sample attrition in controlled treatment trials.** Journal of Nervous and Mental Disease, 135(4):332-337, 1962.

his report considers various ways of dealng with methodological and interpretational roblems due to sample attrition. In treatent trials, subjects are terminated for reatment-related (patient improves or worens) and nontreatment-related (incomplete ata, unwitting change treatment, transfer f the patient, etc.) reasons. Possible onsequences of both types of dropouts on esults are briefly presented. An example, 12-week clinical study of 210 patients, in hich 102 patients were dropped for treatent reasons, is given, along with a table f the cumulative frequency of dropouts. ix partial solutions to the dropout problem re: (1) conduct the study in a research etting rather than on a treatment ward; (2) eplace dropouts; (3) schedule posteva'ua- ion as soon as possible after pretreatment valuation; (4) make maximum use of dropout ata (evaluate dropout at time dropped and se this as final score); (5) regard length f treatment as a covariate and adjust final cores for length of treatment; and (6) use ropouts as criterion data. Dropouts can e kept to a minimum by using well-designed xperiments, based on adequate information f the subjects, treatments, setting, and riterion measures.

Veterans Administration Hospital
Perry Point, Maryland

578 Emmerson, John L. & Miya, Tom S. **Metabolism of phenothiazine drugs.** Journal of Pharmaceutical Sciences, 52(5): 411-419, 1963.

The usual metabolic reaction of the phenothiazine derivatives is sulfoxidation. Further oxidation of the sulfur atom to a sulfone has been observed only with thioridazine. Experiments conducted chiefly with chlorpromazine showed metabolic reactions, such as demethylaction, N-oxide formation, and hydroxylation. Chlorpromazine has much greater potency and a more rapid onset of action than its metabolites, whereas desmethylimipramine is more potent in some respects than its parent compound, and actually may be responsible for the antidepressant action of the latter. Desmethyl chlorpromazine was only slightly less active than chlorpromazine, and chlorpromazine-N-oxide was less active than the latter, though far more active than the sulfoxide metabolite.

Purdue University
Lafayette, Indiana

579 Leitch, A. **Treatment of depression—2.** Nursing Times, 59:69-71, 1963.

In the introduction of this general discussion on the treatment of depression, it is stated that many cases of mild depressions can be and are being treated by a general practitioner, thus eliminating the need for psychiatrists, hospitalization, etc. The different forms of insomnia, present in most depressions, are described, and various drugs for each form are prescribed. The role of the general practitioner in treating mild depression (especially the reactive and neurotic types) is outlined. Any suspected accompanying physical ills should be investigated, since they may be contributing to depression. Drugs to elevate mood in the mild depressions are described, starting from the earlier drugs (amphetamine stimulants) to the use of combinations, and then to the present use of MAO inhibitors. Antidepressants for more severe depressive states, especially in endogenous depression, are briefly listed, along with dosage and side effects. Hospital treatment in very severe depression with suicidal impulses is usually begun with electroconvulsive therapy (ECT), in combination with antidepressants. Drugs or ECT are only part of the treatment, however, and a cheerful surrounding, social activities, occupational therapy, etc., are also necessary. After the acute phase, maintenance dosage should be administered for 2 to 6 months after discharge to prevent relapse.

(No address)

580 Colthart, Shirley M. **Anxiety and its relief.** Applied Therapeutics, 5:153-154, 1963.

Anxiety in the aged that is disturbing to the individual and to others around him may be relieved by tranquilizers. Drugs recommended are: phenothiazine derivatives---chlorpromazine, perphenazine, thioridazine, prochlorperazine, levomepromazine, and trimeprazine; antidepressant drugs---imipramine (sometimes in combination with the phenothiazine group) and monoamine oxidase inhibitors, such as phenelzine; and drugs with a broad range of action, such methaminodiazepoxide and chloroxanthene. The liquid form of the drugs is preferred because it avoids the question of whether or not pills have been swallowed. Gradual rather than abrupt drug withdrawal is preferable for maintaining the patient's improvement. Though useful in younger persons, barbiturates tend to increase confusion in the aged. If hypnotics are required, glutethemide or chloral hydrate are preferred.

Geriatric Centre
Toronto, Canada

581 Katz, Martin M. **Projective techniques and drug research, Chapter 14.** In: Uhr, Leonard. & Miller, James G. Drugs and behavior. New York, Wiley, 1960, p. 501-514.

In definitive research, the utility of drugs in testing specific relationships between personality variables and drug effects is evaluated. Forcing the subject to respond to a concrete task will tend to obscure the more general effects of the drug. DeVos (1952) describes an approach to dealing with affect on the Rorschach Test through the categorization of response content, and providing for scoring the levels of hostility, anxiety, dependency, and positive affect derived from a classification of fantasy content. The high reliability of this approach indicates agreement among the raters as to the content of response. Another objective method, deriving from the interpersonal theory of Sullivan (1947), also is concerned with content analysis. The prime instrument is a rating scale comprised of some 100 descriptive items that can be categorized into eight major classes of interpersonal characteristics.

(No address)

582 Dunham, Richard M. & Howard, Kay. **An effect of research training in the study of psychiatric drug treatment.** American Journal of Psychiatry, 119(8):748-753, 1963.

The present article records the results of a supplementary analysis to a previously published survey of the adequacy of reporting and designing of research, described in 45 articles, on the therapeutic value of tranquilizing and energizing drugs, that appeared in six psychiatric journals in 1957, and in 61 articles published in 1960. Investigators holding only an MD degree accounted for the largest number of articles; they were exclusively responsible for the increase in articles from 1957 to 1960. The frequency for PhD, and "Other Author" categories remained constant. The articles from private practice were significantly and homogeneously lower in methodological ratings than all others except for the "Other" setting. Articles from "Federal" settings were significantly higher in this score than all other types. The implications of these data concern the value of research teams in the study of psychiatric drug treatments. It appears that participation of the PhD's is the primary determinant of methodological adequacy in this work.

NASA-Manned Spacecraft Center
Langley Field, Virginia

583 Sullivan, Philip R. **The general practice of psychiatry.** Rhode Island Medical Journal, 46:83-86, 1963.

A recent survey indicated that somatic methods are primary and psychological methods secondary in present treatment of schizophrenic psychoses in this country. A sample general psychiatric practice is surveyed, and a case history is given of a housewife, 30 years old, who was treated for depression, acute insomnia, and loss of weight. She had been taking 2 mg trifluoperazine b.i.d. and 0.5 g glutethimide daily for 2 weeks when she was interviewed on a crisis-intervention basis by the psychiatrist. She was treated as an outpatient with 25 mg imipramine q.i.d., 10 mg chlordiazepoxide t.i.d., 0.3 g barbital, and 0.2 g sodium amytal daily. The symptoms of depression were explained to her, and she was reassured as to her prognosis. Within a week, she was able to resume care of her home; the symptoms subsided in several weeks; and the medication was tapered off gradually.

Massachusetts General Hospital
Boston, Massachusetts

584 LaVerne, Albert A., ed. **Compendium of neuropsychopharmacology.** Journal of Neuropsychiatry, 4:201-217, 1963.

A portion of the "Compendium of Neuropsychopharmacology," under Section III, Sedatives and Hypnotics, is presented in chart form. Part I of Section III deals with the barbiturates. A brief discussion of the relation of chemical structure to drug activity precedes the chart. In compiling the chart, each research study was considered according to its origin, reliability, patient sampling and numbers, adequacy of controls, and the extent of followup. Data will be revised as the future literature indicates. The following information is included for each drug: generic name, trade name and manufacturer; type and action; indications for use; therapeutic rating (effectiveness, toxicity); side effects; contraindications and cautions; recommended dosage; and references (numbers correspond to bibliography at end of chart). (45 references)

(No address)

585 Chessick, Richard. & McFarland, Robert L. **Problems in psychopharmacological research.** Journal of the American Medical Association, 185(4):237-241, 1963.

The problems encountered in the field of psychopharmacological research are divided

ıto five areas: (1) drugs as independent ıriables; (2) measuring human behavior in ı experimental situation; (3) various fac-ors that interfere with the definition and ıterpretation of the experimental situation; ı) basic statistical procedures; and (5) esign for investigating multivariable prob-ems. Considering drugs as independent vari-ıles, dose-response relationships, equi-ılent doses, and cumulative effect in long-erm therapy have not been defined. In mea-ıring human behavior, a variety of scales ıd measures are used, from which many highly uestionable extrapolations are made. There re three groups of factors that interfere ith control of an experimental situation: 1) the effect of learning the test method ı the subject; (2) metabolic, endocrinolog-cal, and neurophysiological changes, en-ironmental changes, and the subject's trends f thought; and (3) placebo responses based ı explicit or implicit suggestions inherent ı the experimental situation. The stan-ards for a reliable and valid statistical rocedure are given. The design for inves-igating a multivariable problem should in-lude adequate controls, random selection of rugs and subjects, careful selection of riteria, adequate instruction of subjects, ıd allowance for "practice effect" in sub-ects.

3 E. Huron Street
hicago, Illinois

86 Bucci, Luigi. Treatment of some acute schizophrenic syndromes. Psychosoma-ics, 4:157-160, 1963.

eserpine, although it has fallen in disease, s effective in small doses in combination ith chlorpromazine for controlling some chizophrenic symptoms. This combination as been used satisfactorily in over 150 pa-ients. Upon admission, the patient is giv-ı 5 mg of reserpine parenterally once daily ıd 100 mg of chlorpromazine orally t.i.d. eserpine rarely must be given for more than days, but chlorpromazine is continued for ıe length of hospitalization, averaging ess than 3 months, and it may be continued ıereafter on a maintenance dosage. After aking reserpine for 3 days, most patients re free from catatonic excitement or manic eatures, and no degree of depression, which requently develops with large doses, is ob-erved. Patients who had needed some form f restraint became calmer, quieter, more ıoperative, and better related to their en-ironment. Only a few patients developed rowsiness, drooling, or Parkinson-like syn-rome. Though usually classed as tranquili-ers, reserpine and chlorpromazine comprise two different types of drugs: (1) Reserpine stimulates the parasympathetic central sys-tem. Though a strong antipsychotic, chlor-promazine had milder sedative activity than reserpine, and would not improve a patient's condition as fast as when given in combina-tion with the latter.

Rockland State Hospital
Orangeburg, New York

587 Wortis, Joseph. Psychopharmacology and physiological treatment. American Journal of Psychiatry, 119:621-626, 1963.

In this annual review, 114 articles on psy-chopharmaceutical drugs are summarized briefly. Three main topics are discussed. The first topic presents drugs that have shown dangerous physiological side ef-fects---thalidomide, prochlorperazine, chlorpromazine, certain MAO inhibitors, pro-methazine, reserpine, pheniprazine, phenel-zine, nialamid, imipramine, and ampheta-mines. The dangerous side effects result from delayed toxicity due to chronic ad-ministration, addiction, and overdose. The second topic concerns reviews and compari-son studies (particularly of the efficacy of drug therapy and EST). The drugs dis-cussed include fluphenazine, mepazine, pro-mazine, trifluoperazine, chlorprothixine, thioridazine, chlordiazepoxide, carphena-zine, chlorpromazine, prochlorperazine, ami-triptyline, imipramine, nialamid, phenel-zine, tranylcypromine, and haloperidol. The third topic presents new drugs and a brief description of the therapeutic value of each. Drugs discussed include acepro-mazine, protipendyl chlorhydrate, chlorpro-ethazine, a potent new phenothiazine (SKF 7261), a thioxanthen analog of perphe-nazine, butyrylperazine, thioproperazine, butyrophenone carbamide, a mild piperazine phenothiazine (MDS92), cyclopentimine, tet-rabenazine, a benzhydryl derivative (KT-5), a benzoquinolizine derivative (P-2647), benzquinamide, dixyrazine, and a variety of other antidepressants and stimulants.

Jewish Hospital of Brooklyn
Brooklyn 38, New York

588 Wittenborn, J. R. & Plante, Marc. Patterns of response to placebo, iproniazid and electroconvulsive therapy among young depressed females. Journal of Nervous and Mental Disease, 137(2):155-161, 1963.

A controlled method for gaging the efficacy of treatment for depression amoung young

adult females is discussed. A common battery of response criteria was factor analyzed for a placebo group, for a monoamine oxidase inhibitor (iproniazid) group, and for an electroconvulsive-therapy group. Analyses for the placebo and the iproniazid groups were similar in content, and involve three factors each: remission of symptomatic manifestations and dsyphoric mood, energizing of assertive motives as indicated by the Rosenzweig test, and perceptual acceleration as indicated by the Necker cube and the digit-symbol-substition test. Results for the electroconvulsive-therapy group involved five independent factors, four of which were different from the placebo and iproniazid groups: reduction in dysphoric self perceptions, reduction of pathological symptomatology as rated by the treating physician, increase in weight with decrease in assertiveness, decrease in perceptual fluidity, and cognitive loss. Patients respond to electroconvulsive therapy in more different ways than to placebo or iproniazid. In the study of the effect of treatment, criteria variables should be incorporated that represent the response-to-treatment factors that characterize a treatment group.

Interdisciplinary Research Center
Rutgers, The State University
New Brunswick, New Jersey

589 Bordeleau, Jean-Marc. **Insulinotherapie et troubles psychiatriques. (Insulin therapy and psychiatric cases.)** (Editorial) Bulletin of the French-Speaking Medical Association of Canada, 92(2):208-210, 1963.

Because chemotherapy may isolate the psychiatrist from the patient, the contact between patient and doctor afforded by insulin therapy should not be discarded without an adequate substitute. However, numerous works since 1950 indicate that insulin therapy is too dangerous to keep in the arsenal of modern therapeutic measures. Insulin therapy entails the risk of irreversible coma. The criteria for application are as follows: age 16 to 30, male sex, relatively adequate prepsychotic personality, illness with brutal onset or lasting less than 1 year, and without signs of intellectual deterioration. Convulsive therapy under nontraumatic conditions gives nearly equivalent results, whereas insulin without hypoglycemic coma, or before a meal, has no therapeutic value. Mental patients, who consider insulin therapy a last resort, respond poorly, have high physiological resistance, and low percentage of medical discharge, whereas those who accept it as the choice treatment have low physiological resistance and maximum (100%) rate of cure. The percentages of major improvement that have been observed in different treatments are the following: electroshock 54%, lobotomy 46%, insulin 59%, chlorpromazine 82%, reserpine 69%, and control 38%.

(No address)

590 Lai, G. **Modifications des afférences sensitivo-sensorielles lora du traitement aux thymoleptiques. Considérations théoriques et perspectives pratiques. (Modifications of the afferent sensosensory impulses during treatment with thymoleptics. Theorctical considerations and practical perspectives.)** Schweizerische Medizinische Wochenschrift, 93(9):378-381, 1963.

The action of thymoleptics may be defined by their secondary neurological and psychiatric effects---differing in frequency, intensity, and character---according to the dosage and duration of treatment, and reactivity of the individual. These disturbing effects generally involve the psychomotor and psychosensory domains, and the level of vigilance. Surpassing the therapeutic dosage may result in spatial and temporal disorientation and in confusion, although patients do not show the serious signs of intoxication. Amitriptyline has definite soporific action at therapeutic dosage. The "oneiro-confusion syndrome" (syndrome confuso-onirique), usually appearing on the 4th or 5th day, begins with prodromal signs, such as motor restlessness and diurnal and nocturnal oneiric hyperactivity, closely resembling, but less profound than, delirium tremens. The syndrome consists of: (1) trembling, generally limited to the hands, rarely involving the entire body; (2) repeated grasping movements of the hands, directed toward illusionary objects; (3) sensory disturbances, generally visual illusions or hallucinations, rarely auditory; and (4) disturbance of superficial tactile sensitivity and of kinetic sensitivity (dysmetry). In the initial phase, these manifestations appear during diurnal or nocturnal sleep, or during wakefulness. Synthesis of a new thymoleptic, potentiating the effect on sensosensory impulses, is suggested, such as combination of phencyclidine and a thymoleptic.

(No address)

591 Freeman, Joseph T. **Drug therapy in aging patients.** Geriatrics, 18:174-180, 1963.

ntil science is able to confirm or eliminate specific aging factor, it is essential to efine the drugs and methods for those who re aging, as well as those who are now aged. hanges in the aging body influence the se- ection, administration, and actions of drugs ssential to the establishment of physiologic quilibria. The historical development of ttempts to slow down the aging process ap- ears to follow definite lines of precedent, rom transplantation of organ tissues and ells at the beginning of the morphology era n the 18th century, down through the use of rocaine hydrochloride as an intercellular ntropic agent.

omen's Medical College of Pennsylvania hiladelphia, Pennsylvania

92 **To-day's drugs. Tranquillizers.** British Medical Journal, (5350):163-4, 1963.

he classification, pharmacology, and clini- al indications of tranquilizers are briefly iscussed. Reserpine and the phenothiazine erivatives are treated separately. A third roup of drugs of varied chemical composition including meprobamate, benactyzine, hydroxy- ine, chlordiazepoxide, and methylpentynol) s also mentioned.

No address)

93 Cerletti, A. **The hallucinogenic drugs.** Pharmaceutical Journal, Winter Issue: 5-28, 1963.

he author defines hallucinogenic drugs and iscusses their historical aspects as ollows: the isolation of mescaline from a exican cactus; the discovery of LSD; the solation of psilocybin and psilocin from he mushroom Psilocybe mexicana Heim; and he fact that 4-substituted indoles, includ- ng lysergic acid, had special significance, ith reaction markedly different from the -, 6-, and 7-hydroxytryptamine. The metabo- ite theory proposes that small amounts of a resently undiscovered, highly specific etabolite are responsible for the pronounc- d effects of mescaline.

No address)

94 Haase, H. -J. **Möglichkeiten un Grenz- en der Psychopharmakotherapie mit ranquilizern und Neuroleptika. (Possibili- ies and limitations of psychopharmacothera- y using tranquilizers and neuroleptics.)** eutsche Medizinische Wochenschrift, 88(11): 05-514, 1963.

Work of "special importance" in the field of therapy with tranquilizers and neuroleptics (in both theory and in practice) in the last 10 years is surveyed. Tranquilizers are defined as substances that, in addition to a narcotizing, sleep-inducing, intoxicating, or energizing effect, have a special effect upon the psyche. The two groups of psycho- pharmacological agents are classified ac- cording to substances and type of effects. Agents with an antidepressive effect are ex- cluded. Charts are given at the end of the paper. The following data are presented for drugs with tranquilizer effect: short chem- ical designation, psyches effect, therapeu- tic possibilities, and therapeutic limits. For neuroleptics, the data concern the fol- lowing: short chemical designation, trade name, neuroleptic potency (relative to chlorpromazine), and average daily dose to reach neuroleptic effectiveness.

Medizinischen Akademie
Düsseldorf, Germany

595 **Evaluation of psychotropic drugs in private practice.** Diseases of the Nervous System, 24:181-184, 1963.

An evaluation is made to determine the values and the limitations of the drugs available for use in private practice. It was shown that in neurotic depressions, drugs are of minor value since the basic therapy must be directed toward altering life patterns. In treating endogenous depressions (manic-de- depressive) imipramine is the drug of choice. Amitriptyline, used in the treatment of involutional melancholias, is an effective hypnotic when given in 50 mg doses at bed- time. It is an effective tranquilizer when given intravenously in 20 to 30 mg doses. In anxiety-tension states, psychotherapy is the primary tool. Antianxiety agents faci- litate accessibility and communication. Drugs that contain belladonna are used for the sedation of the parasympathetic nervous system; ergotamine tartrate is used for the sedation of the sympathetic nervous system; and phenobarbital is used for the sedation of the central nervous system. Paraldehyde, the barbiturates, glutethimide, ethchlorvy- nol, and the amphetamines are potentially the most addicting of the psychotherapeutic drugs. Chloral hydrate, methyprylon, mepro- bamate, and pheneglycodol are moderately habit forming. Evaluation of drugs is dif- ficult in private practice because of "con- tamination" by the simultaneous administra- tion of other forms of psychiatric therapy.

(No address)

596 Lewis, J. J. **Centrally acting drugs. Part I.** Science Progress, 51(203): 382-398, 1963.

Tranquilizers, antidepressives, and psychotomimetics are employed on a scientifically empirical basis, without any clear knowledge of their precise mechanisms of action in the brain. Some studies have been made of the physiology and biochemistry of the brain to localize the action of transmitter enzymes, and attempts have been made to define the actions of drugs that act on the central nervous system through influence on the synthesis, release, degradation, physiological action, or storage of hypothetical transmitter substances. Acetylcholine, noradrenaline, histamine, 5HT, and GABA are discussed in relation to these physiological biochemical, and pharmacological investigations.

University of Glasgow
Glasgow, Scotland

97 Hollister, Leo E., Overall, John E., Johnson, Merlin, Katz, George, Kimbell, sham, Jr., & Honigfeld, Gilbert. **Evaluation of desi ramine in depressive states.** ournal of New Drugs, 3(3):161-166, 1963.

f 69 newly admitted depressive patients completing a 3-week double-blind study, 32 neurotic depressive and 37 were psychotic depressive. All were males, 20 to 70 years of ge, with median age of 43 years. Most of he patients had a history of previous depressive episodes. Randomly chosen patients ere given one capsule of 25 mg desipramine r of 25 mg lactose t.i.d.; the dosage was ncreased to 100 mg daily for most of the ourse of treatment, never exceeding 150 mg er day. The placebo patients showed significant improvement in depressive agitation, pathy, and retardation on the augemented npatient Multidimensional Psychiatric Scale IMPS), in depression on the abbreviated innesota Multiphasic Personality Inventory, nd on special "manifest depression" scales. esipramine patients showed significant improvement on the IMPS factors for agitation nd motor disturbance, as well as in the MPS "manifest depression" scale. Mean changes in the drug group were generally not as large as in the placebo patients. The group receiving drug showed more statistically significant differences on the IMPS factor for "excitement". A weighted combination of four scales of both tests indicated superiority of placebo over desipramine. Sequential analysis indicated that, after plotting only 11 pairs of patients, desipramine was not going to prove better than placebo. Eight patients showed none of the expected side effects; five patients had delayed urination; and three exhibited hypotension. There were no toxic effects.

Veterans Administration Hospital
Palo Alto, California

598 Frank, Jerome D., Nash, Earl H., Stone, Anthony R., & Imber, Stanley D. **Immediate and long-term symptomatic course of psychiatric outpatients.** American Journal of Psychiatry, 120:429-439, 1963.

Two populations of psychiatric outpatients, 49 in the first population and 60 in the second, were given placebos, and the effect on their reported distress level was noted immediately, and after 1 and 2 weeks on placebo. Patients were 18 to 55 years old, had at least fifth-grade education, and were not currently receiving medication. The patients in both populations received special tests and measures before and after receiving placebo. Over half the patients in each group were reexamined after 3 and 2 years, respectively, at which time some again received a placebo. In both groups, whatever the criterion used or the time interval, a greater proportion of patients reported improvement than reported getting worse. The mean discomfort score dropped sharply during the first interview, before as well as after administration of the placebo, then tended to increase, but not to the initial level. Maintenance on placebo did not increase the effect. The amount of improvement was related to amount of distress reported initially, and symptoms of anxiety and depression showed more improvement than somatic ones. Patients showed little consistency in responsiveness to placebo at different administrations. Various hypotheses to account for the findings are examined, with special reference to the role of cognitions in emotional distress and its relief.

Johns Hopkins University School of Medicine
Baltimore, Maryland.

599 Rosenbaum, M. & Gershon S. **Experiences with a new anti-depressant—amitriptyline.** Medical Journal of Australia, 1:321-325, 1962.

A total of 50 outpatients and inpatients, 36 female and 14 male, 24 to 73 years of age, with average age of 45 years, was selected for this study. The patients were of the following depressive types: endogenous (28), neurotic and/or reactive (19), and schizophrenic (3). The duration of treatment varied from 2 weeks to 9 months. All medication except nocturnal sedation was suspended during the study. The usual dosage administered was 25 mg amitriptyline t.i.d. for 4 days. If no side effects and no improvement were observed, the dosage was increased to 75 mg t.i.d. The dosage

did not exceed 50 mg t.i.d. toward the end of the study for fear of toxic effects. In the overall response, 9 showed marked improvement, 17 showed moderate improvement, 6 showed slight improvement, 16 showed no effect, and 2 worsened during treatment. An overall improvement rate of 75% was obtained in the endogenous depressive group, contrasted to 50% in the reactive depressive group. Improvement was moderate in two schizophrenics and slight in one. The time required for useful improvement varied from 4 days to 6 weeks, the usual time being 1 to 2 weeks. Side effects encountered in 20 (40%) of the 50 patients were usually minor. More serious side effects necessitated cessation of treatment in 3 cases, including one grand mal seizure.

Prince Henry's Hospital
Melbourne, Australia

600 Hekimian, Leon J. & Friedhoff, Arnold J. **Action of large doses of desmethylimipramine on psychotic patients.** Journal of New Drugs, 3(6):367-374, 1963.

The human pharmacology and dose range of desmethylimipramine (DMI) and its effect on depressive symptoms associated with psychosis and on other psychotic symptoms were studied. A monomethyl analog of imipramine, DMI, has been described as a potent agent in the treatment of depression. Fifteen male patients, diagnosed as schizophrenic with prominent depressive features, ranging in age from 20 to 55 years, and with no impairment of physical health, were given initial doses of DMI from 25 to 75 mg daily. Dosage was increased to a maximum of 375 mg daily, at which point toxic effects resulted. DMI did not relieve the symptoms of schizophrenia even at the maximum dose of 375 mg daily. Instead, it activated psychotic symptoms in some schizophrenic patients in doses as low as 150 mg daily. The drug had a mild tranquilizing action in some patients. Of three patients with primary depression of a psychotic degree who received 375 mg of DMI daily, two improved moderately. Besides activating psychotic symptoms in some patients, the drug produced other disagreeable side effects---tremors, hypotension, agitation and restlessness, and drowsiness. The DMI did not produce euphoria or elevate the mood in any of the 15 patients.

New York University School of Medicine
New York, New York

601 Ziporyn, Marvin. **Effective management of delirium tremens.** Applied Therapeutics, 5:137-138, 155, 1963.

Because of the emergency nature of hospital treatment of patients in delirium tremens, no prearranged procedure could be followed. The first 50 of 350 patients, comprising Group I, received: (1) 100 mg i.m. chlordiazepoxide, stat; (2) 25 mg chlordiazepoxide p.o. every 4 hours for 5 or 6 days; (3) 1,000 cc 5% glucose in saline, i.v. stat; (4) Vitamin B complex, i.m. daily; and (5) 4,000 cc sugar fluid p.o. daily. The remaining 300 patients received 100 mg i.m. chlordiazepoxide and 25 mg p.o. every 6 hours for 8 doses (an adjustment of Step 2). Group II (180 patients) was treated as above, with the adjustment in Step 2. Group III (120 patients) was given the above treatment with omission of Step 3. Of the 50 patients of Group I, 49 made an uneventful recovery, and tremors, anxiety, disorientation, and hallucinations disappeared within 24 hours. Oral therapy was continued (150 mg chlordiazepoxide daily) for 5 or 6 days. All the 180 patients of Group II were free from symptoms, except for facial flushing, within 24 hours. In Group III, anxiety disappeared within 24 hours, but all 120 still showed tremor, hallucinations, impairment of sensorium, and elevated temperature for 3 or 4 days. No toxicity or side effects were noted.

Cook County Hospital
Chicago, Illinois

602 Hollister, Leo E., Overall, John E., Kimbell, Isham, Jr., Bennett, J. L., Meyer, Fred, & Caffey, Eugene, Jr. **Oxypertine in newly admitted schizophrenics.** Journal of New Drugs, 3(1):25-31, 1963.

Forty-nine newly admitted schizophrenic patients completed a 6 weeks' course of treatment. Their diagnoses included: paranoid 23, unclassified 15, other types 11. Median age was 34 years, and the age range was 21 to 50 years. Median duration of their present illness was 8 weeks and that of total illness was 312 weeks. Oxypertine was administered in 20 mg tablets t.i.d., and was increased weekly to a mean daily dose of 165 mg in the last 3 weeks. Minimal doses of barbiturates, chloral hydrate, and anticholinergics or antihistaminics were permitted. No control treatment was used. Comparison of change scores on the Brief Psychiatric Rating Scale showed that oxypertine produced effects on total pathology comparable to those of acetophenazine and perphenazine. Electronic computation of each patient's diagnostic type yielded a classification of 8 paranoid, 18 depressive, and 23 schizophrenic. The change in total pathology was significantly greater in the schizophrenics than in the paranoid, and

gnificantly greater in the depressive than
the paranoid groups. There was no sig-
ificant difference in total response of the
epressive and schizophrenic classifica-
ions. Side effects were not of major im-
ortance, and 29 patients had no side ef-
ects. One or more features of the Parkin-
on syndrome were found in 23 patients, agi-
ation occurred in 15, anxiety occurred in
, and drowsiness occurred in 11.

eterans Administration Hospital
alo Alto, California

03 Hare, Henry P, Jr. **Comparison of diazepam, chlorpromazine and a placebo in psychiatric practice.** Journal of ew Drugs, 3(4):233-240, 1963.

n a double-blind crossover study, 49 subects, including 17 men and 32 women, 18 to 5 years old (average age 36.6 years), were elected from psychiatric practice. Their iagnostic categories were depressive anxiety, depression, manic depressive, and chacter disorders. Approximately half of the roup received a placebo for 1 week, 25 mg hlorpromazine for 3 weeks, another placebo or 1 week, and 5 mg diazepam for 3 weeks. he other subjects received diazepam before eceiving chlorpromazine, but maintained the ame schedule. Results showed that when iazepam was administered as the first active agent, almost the same number of paients had like response to both active mecications, although full symptomology reurned during the intervening week on placebo. When diazepam was given as the last ctive agent, the overall responses and imrovement of individual symptoms were coniderably better. Only three patients showd the same response to both active drugs. ide effects occurred with the active agents nd with the placebo. The side effects of iazepam were similar to, but more severe han, those of chlorpromazine, e.g., atigue, drowsiness, hypoactivity, and dryess of mouth. Therapy was discontinued in ne instance because of intolerance to iazepam at a dosage of 5 mg per day. There ere no toxic reactions or systemic dysunction on any agent at the dosage used.

ulsa Psychiatric Foundation
ulsa, Oklahoma

04 Hollister, Leo E., Bennett, J. L., Kimbell, Isham, Jr., Savage, Charles, Overall, John E. **Diazepam in newly admitted schizophrenics.** Diseases of the Nervous ystem, 24(12):1-4, 1963.

In the first of two studies, 25 patients were selected, all but 4 being diagnosed as schizophrenic reaction though not severely psychotic. The patients, all males, with a median age of 37 years, were given 20 to 80 mg (40 mg median) diazepam daily for 6 weeks. The clinical impression was that 9 improved, 7 were essentially unchanged, and 9 became worse. Mean reduction in total morbidity with diazepam was substantially less than that ordinarily obtained with the phenothiazines. Dizziness and overt sedation were the most frequent side effects, and withdrawal reaction occurred in one patient. On this basis, diazepam is not very useful in treating schizophrenics. The second study concerned 33 newly admitted schizophrenic males with median age of 36 years, duration of present illness 10 weeks and of total illness 10 years. Treatment consisted of 30 mg diazepam p.o. or i.m. daily for the first week, 60 mg the second week, and 80 mg the third week. Doses were flexible during the final 3 weeks, and the mean daily dosage was 100 mg. No sedatives or drugs for extrapyramidal syndromes were allowed. The "paranoid" patients actually appeared to worsen after treatment, whereas the other types of patients improved substantially. Drowsiness and dizziness were the most frequent side reactions. Withdrawal reaction occurred in 6 of 13 patients upon being switched from the drug to placebo.

Veterans Administration Hospital
Palo Alto, California

605 Frignito, Nicholas G. **Maladjusted young social wards treated with hydroxyzine hydrochloride.** Diseases of the Nervous System, 24(10):620-623, 1963,

An 18-month clinical investigation was made of 53 patients, 16 boys and 37 girls, from 2 to 18 years old, in an agency setting. The majority were organically normal and of normal intelligence. Of 35 with adjustment reactions, 6 had depressive features, and the others included childhood autism, mental deficiency, schizophrenia, psychoneurosis, affective psychotic reaction, passive aggressive personality, and behavior disorder. Psychotics with assaultively aggressive symptoms were dropped from the study, and those remaining were moderately or mildly disturbed, with a fair to good prognosis. The dosage of hydroxyzine hydrochloride was adjusted to individual response, with the majority receiving 10 to 150 mg daily, in divided doses. The patients received the drug for 3 months to 2 years. Of the 53 patients, 28 (53%) were greatly improved; 11 (21%) recovered; and 14 (26%) failed to improve.

Enuresis was effectively controlled in all but four children in the failure group. Of the 14 failures, 4 were psychotic, 3 were mentally defective, and 6 had behavioral disorders. There were no toxic effects, and drowsiness was observed in only 5 patients, requiring a reduction in dosage.

(No address)

606 O'Leary, J. A clinical investigation of methohexital sodium. Medical Journal of Australia, 1:594-595, 1962.

Methohexital sodium was investigated clinically. All patients were chosen at random. The premedication appropriate to the proposed operation was given, and 100 mg methohexital was rapidly injected i.v. In 43 cases, the time from the end of injection to no response to spoken word was 2 to 45 seconds, with an average of 21.6 seconds. The time from the end of the injection to response to an auditory command ranged, in 11 cases, from 1 to 7.5 minutes, averaging 4.7 minutes. In 11 cases, the fall in minute volume of respiration was 60% of the original. Blood-pressure changes in 43 cases averaged 25 mm of mercury (systolic). The majority of 12 patients showed an average increase in pulse of 25 beats per minute. Of the 43 patients, 3 exhibited muscle contractions on losing consciousness, and 6 complained of pain during the injection. One patient developed severe laryngospasm. A smooth methohexital, nitrous oxide-oxygen and relaxant technique was impossible because of the ultrashot action and sharp endpoint of the drug. Doses up to 600 mg were needed in procedures lasting 30 to 40 minutes. In clinical evaluation, methohexital had no significant analgesic effect, and it may have an antianalgesic effect.

St. Vincent's Hospital
Sydney, Australia

607 Leblanc, J., Lemieux, L., Cote, F., Desbiens, A., & Blanchet, A. **The cold pressor test in mental patients during tranquilizer therapy.** Medicina Experimentalis, 8:163-170, 1963.

A group of 25 psychotic patients, including 14 schizophrenics who had never been hospitalized nor received intensive tranquilizer therapy, was maintained on tranquilizers, mainly of the phenothiazine group, for at least 1 month, and subjected to two types of tests. Test groups of 25 epileptics and 10 normal subjects also were used. Skin tests made with 1 gamma of histamine base before, and 1, 2, and 4 weeks after hospitalization showed that mental patients have lowered response to histamine increased in all patients after 1 week of tranquilizer treatment. This response was maintained by a group of discharged patients, but fell back to the initial level in those remaining in the hospital. The cold pressor test consisted of immersing one hand in water at 4° C for 3 minutes, and of taking blood-pressure readings every minute. The average increase in systolic pressure after immersion is essentially normal in epileptics and nonschizophrenics, but the blood-pressure response is very weak in schizophrenics. This response increases significantly in schizophrenics after tranquilizer therapy. Both diastolic and systolic pressure were within normal limits in the schizophrenic group at admission, but dropped 10 to 15 mm mercury after 1, 2, and 4 weeks of hospitalization. Urinary determination of adrenaline, noradrenaline, and 5 HIAA showed no difference before and after tranquilizer therapy.

School of Medicine
Laval University School of Medicine
Quebec City, Canada

608 O'Brien, Cyril C. **Intensive calcium therapy as an initial approach to the psychotherapeutic relationship in the rehabilitation of the compulsive drinker.** Journal of Psychology, 57:125-129, 1963.

To eliminate the physiological impairments concomitant with compulsive drinking, and to make alcoholics amenable to psychotherapy, 234 alcoholics were given paraldehyde, glucose, and Vitamin B therapy during a 2-year hospital study. The mean lying-in period for the 175 hospitalized drinkers of this group was 5.2 days. The results of intensive calcium therapy, consisting of i.v. administration of a buffered mixture of calcium chloride, potassium chloride, sodium chloride, sodium lactate, dextrose, and water, were studied in another group of 261 compulsive drinkers. The usual dosage was 20 cc i.v. b.i.d. for 14 days, and then tapering off until a total of 25 injections had been given. Intensive calcium therapy is escharotic, necessitating i.v. administration. As a result of the intensive calcium therapy, only 25 of the 261 patients required "lying-in", and the average hospitalization time was reduced to a mean of 2.0 days. The characteristic trembling of hands was eliminated in 12 minutes to 4 hours, with a mean of 30 minutes. Of the 261 patients, about 75% were permanently rehabilitated.

arquette University
ilwaukee, Wisconsin

09 O'Connor, A. & MacIntyre, I. M. Controlled clinical trial with prothipenyl hydrochloride ("Tolnate") as a premedication in anesthesia. Journal of the Royal aval Medical Service, 49:28-32, 1963.

he results of a double-blind study showed rothipendyl hydrochloride to be effective s a premedication sedative, as well as beng satisfactory in preventing postoperative ausea and vomiting. The patients, 16 to 60 ears old, were, except for their specific ondition, healthy. Thiopentone was used or induction, followed by either helothane r trilene with pethidine, and with relaxnts as required. In a pilot study, 30 paients were given 40 mg i.m. of the test rug on completion of the operation. Only he man vomited, and he previously had sere postoperative emesis. In the main tudy, 98 patients were premedicated with 15 g morphine sulfate and 0.6 mg atropine sulate, and 98 patients received 40 mg propipendyl hydrochloride and 0.6 mg atropine ulfate 1 hour before the operation. Nausea ccurred in 19 (19.4%) and vomiting occurred n 14 (14.3%) of the morphine group, whereas ausea occurred in 9 (9.2%) and vomiting ocurred in 1 (1%) of the test-drug group. he degree of tranquility of patients arrivng in the operating room was much the same n both groups. No difficulties were encountered during anesthesia in either groups. he preoperative sedative-hypnotic effect as good in both premedications, but prothiendyl hydrochloride was more satisfactory n the postoperative period. Only one paient, who had been oversedated with the rug, became violent in the postoperative eriod.

No address)

10 North, William C., Collawn, Thomas H., Hudnell, A. B., Jr., & Stephen, C. R. actors concerned with postoperative emesis nd its prevention with thiethylperazine, ournal of the American Medical Association, 83(8):656-658, 1963.

hree double-blind studies were made of the fficacy of thiethylperazine in controlling ostoperative emesis in unselected surgical atients over 5 years old. In the first tudy, 10 mg (5 mg for ages 5 to 12) of the rug or a placebo were injected i.m. 30 inutes before completion of the operation. f the 710 patients given thiethylperazine, 2.6% vomited, and emesis occurred in 54.4% of the 680 control patients during 24 hours. There was little difference between the two groups after 4 hours. In the second study, patients were given either 10 or 20 mg of the drug or placebo. Twenty-two percent of the 572 control patients vomited, and 16.6% of the 482 patients given 10 mg of the drug and 19.5% of the 282 patients given 20 mg of the drug vomited within 2 hours. In the third study, in ocular surgery 6 injections were given, beginning 30 minutes before completion of the operation and every 4 hours thereafter. Half the patients received 10 or 20 mg of the drug, and the other half received the control solution. Thirteen percent of the treated and 32% of the control group vomited. In the second study, thiethylperazine was more effective with the anesthetics that have greater frequency of vomiting (ether or cyclopropane), but was ineffective in patients receiving thiopental-nitrous oxide or spinal anesthesia. Incidence also varied with the operative site, duration of anesthesia, and age of the patient. Considered by race, 13.2% of 136 control Negroes vomited, contrasted to 25.2% in 436 control whites. With the exception of the Negro female, thiethylperazine was strikingly effective in reducing emesis.

Duke University Medical Center
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611 Lehmann, M. M. Résultats cliniques de l'utilisation d'un nouveau spasmolytique: La propyromazine. (Clinical results of the use of a new spasmolytic: Propyromazine.) Lyon Medical, 48:1133-1136, 1139-1141, 1962.

On the basis of 16 months' experience with propyromazine administered orally, this drug appears very effective, has excellent tolerance characteristics, and has no important side effects. A total of 62 observations were made, mainly in cases of biliary pathology. In 61 cases, 25 mg tablets were used as a spasmolytic, 75 to 100 mg per day, or as an analgesic, 25 or 50 mg during pain. The injection form produced very incomplete sedation in one hepatic colic case. Drowsiness was observed in only one case. Drug efficacy is, on the whole, remarkable. Excellent (E), good (G), or no (N) results were obtained as follows: gall stone with drug used as treatment, E 6, G 4, N 4; with drug used as sedative, E 4, G 2, N 1; biliary dystony (biliitis?), with drug used as treatment, E 1, G 5; with drug used as a sedative, E 5, G 3, N 1; post-cholecystectomy syndrome G 2, N 2; pancreatitis G 2, N 1; simple spastic colitis E 4, G 1, N 11 and

fairly diverse miscellaneous cases E 9, G 3, N 2.

(No address)

612 Imlah, Norman W. **Preliminary report on phenoxypropazine.** American Journal of Psychiatry, 119:1091-1092, 1963.

Phenoxypropazine, the first monoamine oxiddase inhibitor to be developed in Britain for clinical use, was tested on 24 outpatients with depression. Of the 20 patients who completed the study, 16 were female and 4 were males, aged 29 to 60 years, with mean age of 44.4 years. Duration of illness was 1 month to 2 years. All were started on 10 mg phenoxypropazine b.i.d., and 13 remained on this dosage for the balance of the study. At the end of the third week, 5 patients were increased to 10 mg t.i.d., and 2 patients were decreased to 5 mg t.i.d. The only other drugs given were barbiturates at night. At the end of 6 weeks, 6 patients were free of symptoms; 6 showed minor symptoms only; 2 were improved; and there was no change in 6 patients. Improvement began before the end of the first week in 3 cases, and began in the remaining 17 cases during the second week. One case was discontinued because of diarrhea on the second day of treatment. The drug was stopped on the 6th day, and the diarrhea disappeared. Five patients reported minor and transient symptoms, such as nocturnal limb jerking, severe headache after alcohol, mild dizziness, nausea, dry mouth, and nocturnal frequency. Phenoxypropazine seemed to have considerably less hypotensive action than that produced by other monoamine oxidase inhibitors.

Uffculme Clinic
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613 Smith, Marshall E. **The effects of benzquinamide.** Diseases of the Nervous System, 24:116-121, 1963.

In a critical analysis of benzquinamide, a double-blind, crossover technique was employed, in which all aspects were compared with chlorpromazine, meprobamate, and chlordiazepoxide. Sixty psychoneurotic patients were selected from private practice, 27 males and 33 females, 17 to 59 years old, all of whom reported subjective anxiety. Identical capsules were given, each containing 50 mg benzquinamide combined with 400 mg meprobamate, or 25 mg chlorpromazine, or 10 mg chlordiazepoxide. Starting dosage was one capsule t.i.d., and ranged from 3 to 14 capsules per day during the treatment. At the end of 6 weeks, no medication was given for 1 week, and then the second medication was given for 6 weeks. Seven males and 13 females, with an average age of 34.9 years, received the benzquinamide—chlorpromazine combination; the same sex distribution, with an average age of 39.6 years, received benzquinamide—meprobamate; and 13 males and 7 females, with an average age of 31.7 years, received benzquinamide—chlordiazepoxide. Benzquinamide was found to be more effective than, or equal to, the other drugs in remission of symptoms, particularly that of anxiety. It was surpassed only by chlorpromazine in treatment of hostility. Each test group showed a similar pattern, regardless of the previous combination of medication. Benzquinamide produced drowsiness in 4 patients, Parkinson-like syndrome in 2 patients, and weakness in 4 patients. Benzquinamide compares favorably in wide effects with those of meprobamate.

(No address)

614 Winslow, Walter W. **Narcotherapy with methohexital sodium.** American Journal of Psychiatry, 119:886-887, 1963.

Methohexital sodium, an ultrashort-acting barbiturate for i.v. use, is approximately three times as potent as thiopental sodium by weight, and is metabolized, by the liver, 50% faster than thiopental. The technique, indications, and contraindications are very similar to those encountered with amobarbital and thiopental sodium. At the rate of 1 cc per 5 pounds, 20 to 30 cc of 1% methohexital solution is injected into the antecubital vein. The average person requires 5 to 8 cc (50 to 80 mg) for narcotherapy. Because recovery is rapid, the interview may be resumed after a few minutes' wait if too much drug is injected. The patient regains almost full consciousness in 15 to 20 minutes, and only a mild feeling of drowsiness has remained longer than 20 minutes. No prolonged drowsiness, confusion, nausea, or vomiting were encountered. In all cases, the verbal productions of the patient were entirely comparable with what might be obtained with either amobarbital or thiopental sodium.

Veterans Administration Hospital
Cincinnati, Ohio

615 Barbour, J. Pius, Jr. **Maintenance therapy of chronic psychotics with perphenazine.** American Journal of Psychiatry, 120:176-177, 1963.

he results obtained in treatment of 200 utpatients with perphenazine for 1 to 9 onths are generalized. The patients were omen, 20 to 50 years old. All had chronic sychoses, and most were schizophrenics. he usual starting dosage of 16 mg t.i.d. as reduced to 8 mg t.i.d. after 1 week, hen gradually decreased to 4 mg t.i.d. fter 3 to 6 months. Eighty percent of irst-admission patients were discharged r considerably improved, and 70% of those ho had one or several previous admissions howed favorable response. Of those re- urning to the same hospital with relapse, 0% had discontinued therapy for at least months. Pseudoparkinsonism was the only ignificant side effect, usually occurring n the few who had received more than 16 mg .i.d. Other side effects were minor and ccurred in less than 1% of the subjects. t was necessary to discontinue perphena- ine in only 4 patients. All patients also eceived psychotherapy, and it is impossible o isolate the degree of improvement due to he drug from that due to the therapist. any chronically ill patients may now be reated with perphenazine maintenance thera- y on an ambulatory basis.

utpatient Department of the Philadelphia tate Hospital
hiladelphia, Pennsylvania

16 Padula, Louis J. & Karliner, William. **Inhalation Indoklon convulsive ther-** py. Journal of Neuropsychiatry, 4:182-183, 963.

onvulsion therapy using inhaled hexafluoro- iethyl ether produced improvement in 89 of 2 patients. The subjects ranged from 18 to 8 years of age; most were hard-core sub- ects with psychotic episodes of 5 months to 8 years. Of the 89 schizophrenics in the roup, 16 returned to their premorbid per- onality, 70 were improved, and 3 were nimproved. Three manic-depressive patients eturned to their premorbid personality. wo cc of hexafluorodiethyl ether were laced in the vaporizer, and then enough nesthetic agent, usually 6 to 8 cc of a percent sodium brevital, was administered o produce sleep; this was followed by 15 to 0 mg succinylcholine chloride. Using a ubber oralpharyngeal airway, the mask was eld firmly on the face to prevent leakage, nd the bag gently squeezed 3 to 4 times in he space of 20 seconds. The myclonic move- ents were followed by a relatively short onic phase, and then by a prolonged clonic hase of about 1 minute. Preventilation ith oxygen plus hexafluorodiethyl ether revented post-treatment apnea. Excessive post-treatment excitement was controlled with i.v. injections of 3-3/4 or 7-1/2 grains sodium amytal, and subsequently, by 50 mg chlorpromazine i.m. 10 minutes prior to treatment. Hexafluorodiethyl ether should not be given in the presence of any disease of the upper respiratory system.

West Hill Sanitarium
Riverdale, Bronx, New York

617 Houillon, Salles, & Selin. **Problèmes poses par une ingestion massive de tabac chez un melancolique senile. (Problems posed by massive ingestion of tobacco by a melancholic senile.)** Annales Medico Psychologiques, 2:60-63, 1963.

A presenile, arteriosclerotic, delirious male, 71 years old, with anxiety and persecution complex, attempted suicide following transfer to a chronic ward by swallowing 40 cigarettes, equal to 40 g tobacco, between the evening meal and breakfast. Vomiting was followed, during the next 2 hours, by four epileptic seizures with the usual phases, but with difficult recuperation. The intervals were marked by intense dyspnea, palor, rapid pulse, pronounced drop in blood pressure, total disorientation, and aphasia. Hemiplegia occurred for a few hours, but right facial loss was more prolonged. The patient was given 0.20 gardenal, hypertonic glucose serum infusion, scurocaine, solurutine-papaverine, i.v. aminophylline, i.m. specilline, and classic cardiotonics. The signs of cardiovascular deficit disappeared, blood pressure regained equilibrium, and appetite and sleep returned to normal. The paretic signs disappeared without sequel, and no other neurological disturbances were noted. A total of 400 to 600 mg nicotine and nornicotine, the only significant toxic agents in cigarettes, was ingested. Although the fatal dosage is 30 to 60 mg, fatality was avoided, probably because the stomach was filled with food, its rhythm was very slow, and vomiting of the tobacco avoided fatal concentration in the blood. The most important element was the drop in blood pressure caused by cerebral ischemia. Lack of significant ECG and EEG indicates absence of coronary or cerebral ischemia, suggesting a particular case of toxicity, varying according to certain indeterminable factors of nicotine at the level of the central nervous system.

(No address)

618 Teitelbaum, I. **Electrocardiographic changes associated with phenothiazine.** (Letter) Lancet, 1(7272):115, 1963.

Characteristic features were found in the ECG of approximately 30% of patients of different ages who had received phenothiazine for different periods of time. These features were: low voltage in the standard leads with widening of QRS complexes; flat or isoelectric T, especially in AVL; and inverted T in the right precordial leads. The ECG returned to normal after treatment was stopped. No known pathological or pathoanatomic reason for this pattern could be found.

Malben Hospital
Shaar-Menashe, Israel

619 Moreigne-Laval, M. O. **Contribution à l'etude clinique d'un nouveau neuroleptique phenothiazinique. (Contribution to the clinical study of a new neuropleptic: phenothiazine.)** (Abstract) Annals of Medical Psychology, 122(2):286-287, 1964.

The effects of R.P. 8909 were studied in 51 patients, 16 to 80 years of age, with dossages of 15 to 60 mg (average 30 mg) t.i.d. Tolerance generally was good. Eleven psychoses and neuroses were observed in senile and cerebral arteriosclerotic cases. A thymic disturbance definitely was involved in some cases; thus, the effects of a neuroleptic are not surprising, and specialization for psychoses need not be ascribed to these drugs. The results were satisfactory in epileptics; results resembling those produced by drugs with fading effects were obtained with oligophrenics after brief treatment. In asthenic and anxiety states, sedation and a certain euphoric action are noted. In depressed states, R.P. 8909 could prepare the action of specific drugs by first controlling the agitation of anxiety. In chronic delirium, it may follow a prescription of largactil. Although the action of the product appears established, its specificity in neuroses is less defined. It is not emphasized in the literature, but edema of the inferior extremities is not rare.

(No address)

620 Denber, Herman C. B., Teller, David N., & Kauffman, Dorothy. **Studies on mescaline XIV: (Comparative biochemical effects of different drugs.)** Diseases of the Nervous System, 24:302-303, 1963.

In an extension of an earlier report, 6 drugs were injected prior to intravenous mescaline in 68 patients: thioperazine in 11 patients, chlorpromazine in 11, haloperidol in 10, sodium amytal in 10, diethazine in 12, dl-amphetamine sulfate in 11, and saline solution in 3 control subjects. The drugs were grouped according to their blocking action with regard to the decrease in levels of ninhydrin positive substances and inhibition of the clinical mescaline-induced state. Thioperazine and chlorpromazine were most effective, haloperidol was moderately effective, and amytal and saline were ineffective, whereas diethazine and amphetamine intensified the reaction. In the first two groups above, increases in blood glucose due to mescaline, usually occurring within one-half hour after its administration, were delayed and limited to less than 50%. The psychotropic drugs, such as chlorpromazine and thioperazine, by altering membrane permeability may prevent both the entrance of mescaline and its action on cellular metabolism.

(No address)

621 Karliner, William. **Clinical experiences with intravenous Indoklon: A new convulsant drug.** Journal of Neuropsychiatry, 4:184-187, 1963.

A 10% solution of hexafluorodiethyl ether is more practical than the 5% solution previously used, as it induces seizure within 40 seconds; enables use of a wider needle (22 gage, instead of 20 gage) and the use of 30% to 50% less solution; permits injection in 30 to 40 seconds, thereby giving maximum muscle relaxation with the use of succinylcholine chloride; and causes very little, if any, sclerosis of the injected veins. It is important to halt i.v. administration of hexafluorodiethyl ether as soon as myoclonic twitching appears, or secondary seizures will occur. Thirty patients (24 females and 6 males) 18 to 62 years of age (average age 36 years) were observed from 3 to 15 months and treated on an ambulatory basis. Of 14 who suffered from schizoaffective psychoses, one did not improve (further treatment refused after 2 hexafluorodiethyl ether injections), 7 returned to their premorbid personality, and 6 appeared better; all 6 paranoid schizophrenics were somewhat improved; 3 of the 5 manic patients returned to their premorbid personality, and 2 were considered improved; of the 5 depressed, 3 showed improvement, and 2 returned to their premorbid personality. Generally, all patients react the same to hexafluorodiethyl ether as to electroconvulsive therapy. Nausea may occur in some patients; it may be minimized by 50 to 10 mg prochloperazine or 25 to 50 mg chlorpromazine i.m. before, or

mmediately after, treatment. No complica-
ions have been observed during treatment
ith hexafluorodiethyl ether.

est Hill Sanitarium
iverdale, Bronx, New York

22 Friedhoff, Arnold J. & Hekimian, Leon. A pilot study of Win 18,501. Diseases f the Nervous System, 24:241-242, 1963.

pilot study of a tranquilizing drug, 4-
henylpiperazine hydrochloride (Win #18501)
s conducted with six male schizophrenic
tients, ranging in age from 22 to 45 years.
his drug represents a new class of com-
unds, the alkyl indolyl ethyl 4 phenyl-
perazines, which have less adrenolytic ac-
on than the phenothiazines. Treatment was
itiated with 20 to 40 mg of the drug daily,
th dosage increased until evidence of tox-
city resulted. Daily dosage ranged from 20
260 mg; cumulative dosage ranged from 200
3,500 mg. The drug was more stimulating
d agitating than tranquilizing. Side ef-
cts include extrapyramidal signs, agita-
on, and hyperactivity, ataxia, pallor,
urred speech, hypotension, and dry throat.
boratory tests were normal, except for
me increase in eosinophiles in two patients.

w York University School of Medicine
w York 16, New York

3 Margat, P. & Créton, M. Correction des chutes tensionnelles dues aux neuleptiques par le chlorhydrate de M-éthylino-éthanol-phénol-racémique. (Correction neuroleptic-induced drop in blood pressure th racemic methylaminoethanol chlorhydrate.) nales Medico-Psychologiques, 121:473-475, 63.

drop in blood pressure connected with neu-
leptic therapy may indicate a state of
rdiovascular collapse. A daily dose of
cemic m-ethylamino-ethanol-phenol chlorhy-
ate, three times larger than the dose usu-
ly prescribed, is used to correct the ef-
cts of hypotensor agents when taken in
bstantial daily amounts, such as chlorpro-
zine 150 mg per day. Administration of
uroleptics to 39 patients showed various
grees of drop in arterial pressure in the
jority of cases. Racemic m-ethylamino-
hanol-phenol chlorhydrate administered in
sage of 30 drops resulted in an increase
arterial pressure of at least 0.5 mm
rcury in 18% of the patients, no change in
%, and a further drop in 24%; 60 drops
oduced an increase in 12%; no change in
%, and a drop in 28%; 100 drops resulted in an increase in 76%, and no change in 24%. No toxicity was noted at these dosage levels. Clinical observation indicated no psychotonic action of the drug.

(No address)

624 Settel, Edward. A clinical evaluation of benzquinamide with observations on the total activity potential. Clinical Medicine, 70:957-962, 1963.

A total of 54 patients (15 men and 39 women) were treated for 2 to 14 weeks with benzquinamide in a single-blind study. The ages of the patients were 38 elderly, 6 under 40, and 10 between 40 and 55. Symptoms included agitation, fear, confusion, childishness, depression, and irritability. The daily dosage of benzquinamide was 50 to 400 mg p.o. Improvement began within 24 to 48 hours, and excellent or good improvement was obtained in 45 patients (83%). The most notable therapeutic effect was the relief of, or marked reduction in, agitation and anxiety. The substitution of placebo produced a relapse in 12 of 13 patients within 48 to 72 hours. No toxic effects and side effects, other than transient drowsiness and vertigo, were observed. In four patients with Parkinson's disease receiving 50 mg benzquinamide t.i.d. concomitantly with anti-Parkinson agents, improvement of tremor, of rigidity, and of speech persisted, even after withdrawal of the anti-Parkinson agents.

Brooklyn, New York

625 Brock, Joseph T. & Dyken, Mark. The anticonvulsant activity of chlordiazepoxide and Ro 5-2807. Neurology, 13:59-65, 1963.

The relative effectiveness of chlordiazepoxide, Ro 5-2807, and four control medications (blank, 50 mg of phenobarbital, 100 mg of diphenylhydantoin, and 100 mg of phenobarbital) as anticonvulsants was studied in 27 adult epileptic patients of both sexes. A method for determining the effectiveness of the medications in controlling motor seizures of patients with focal brain damage and epilepsy is presented. The method permits a statistical determination of the reliability of any impressions based on differences among the responses to various medications and doses. Doses of 10 and 25 mg of chlordiazepoxide given orally t.i.d. for 3 days decreased the frequency and intensity of motor seizures in the test patients. Doses of 5 and 10 mg Ro 5-2807, given in the same manner, also decreased seizures. Prolonged

therapy with chlordiazepoxide may lead to tolerance or addiction. Intoxication and mental confusion can occur with doses in excess of 80 mg per day. The similarity of Ro 5-2807 to chlordiazepoxide makes this drug also suspect. The results of this study apply only to short-term treatment.

Indiana University Medical Center
Indianapolis, Indiana

626 Donovan, John. **Radiation sickness and its control with thiethylperazine ("Torecan"): A preliminary evaluation.** Medical Journal of Australia, 1(17):614-615, 1963.

Thiethylperazine maleate was tested as an antiemetic in cases of radiation sickness following deep X-ray therapy. This drug is a member of the perazine series of phenothiazine drugs. Thiethylperazine differs from the other members of the series in that it is a specific antiemetic, without tranquilizing properties or the tendency to induce extrapyramidal effects. Patients for the drug test were restricted to those receiving heavy doses of irradiation and among whom vomiting would be expected. Seventy-seven patients were tested, 31 with carcinoma of the breast, 30 with abdominal or pelvic neoplasms, 4 with thoracic neoplasms, 7 with bone disorders, and 3 with neoplasms of the head. Patients were given 4,000 to 4,500 roentgens. Thiethylperazine was given in a standard dosage of one tablet t.i.d. Complete relief from nausea and vomiting was obtained by 48 patients, and partial relief was obtained by 23; treatment was ineffective in 6 patients. The majority of patients had no side effects from the drug; absence of drowsiness was a striking feature. One patient, an 18-year-old boy who received irradiation of the skull, developed spasms of the jaw muscles, which subsided when thiethylperazine treatment was suspended.

Royal Prince Alfred Hospital
Sydney, Australia

627 Khanna, J. L., Pratt, Steve, Burdizk, E. G., & Chaddha, R. L. **A study of certain effects of tranylcypromine, a new antidepressant.** Journal of New Drugs, 3: 227-231, 1963.

A double-blind study of 30 female patients was conducted to determine the effects of tranylcypromine, and antidepressant, on the ego strength, anxiety, depression, and hospital adjustment of depressed persons. The patients were selected at random, and their age range was from 24 to 47 years. The sample was randomly divided into two groups of 15 each to constitute the control and experimental groups. Placebo and tranylcypromine were administered to the two groups for 2 weeks in dosages of 30 mg daily, 20 mg in the morning and 10 mg in the afternoon. Depression was measured by the depression scale of the MMPI, anxiety was assessed with the Taylor anxiety scale, and ego strength was determined with Barron's ego-strength scale. The administration of tranylcypromine increases a person's ego strength and decreases depression and anxiety; these effects continue even when the drug is discontinued. The drug does not appear to affect the hospital adjustment in any appreciable manner. An attempt was made to develop a criterion that may be helpful in determining if tranylcypromine can produce statistically significant results for a new patient. A discriminant function, y, was computed, and its value was found to be equal to or less than -0.4365.

University of Tennessee
Memphis, Tennessee

628 Sadowsky, A., Pfeifer, Y., Sadowsky, E., Tsur, C., & Sulman, F. G. **Serotonin metabolism in habitual abortion.** Obstetrics and Gynecology, 22(6):778-781, 1963.

Daily urinary levels of the serotonin metabolite 5-hydroxyindoleacetic acid (5-HIAA) were determined in pregnant women with a history of normal pregnancies, women suffering from habitual abortion (in whom a psychic component was suspected), and women on the day of abortion in order to elucidate the existence of a relationship between serotonin production and the course of pregnancy. Average urinary excretion of 5HIAA in normal pregnant women is 5.6 mg per day. In women who suffer from habitual abortion of suspected psychogenic origin, the average excretion is 8.9 mg per day. The 5HIAA excretion in habitual abortion cases reached peak values of 30.0 to 40.0 mg per day during the second through fifth months of pregnancy---the period in which abortion had occurred in previous pregnancies. Increased serotonin production may be responsible for habitual abortion, since serotonin is known to contract the uterus, the placenta, and the umbilical cord vessels.

Rothschild-Hadassah University Hospital
Jerusalem, Israel

629 Gucker, Donald K. **Combining external and internal symbolization in the LSD episode.** Journal of Psychology, 55:401-408, 1963.

)-lysergic acid diethylamide (LSD-25) may be ised as an adjunct to long-term psychoanaly-tically oriented psychotherapy in certain patients not amenable to usual therapeutic approaches. The hallucinatory material pro-luced in the LSD episode is markedly similar to dream symbolization. Defensive symbol-ization takes place in presence of the pa-tient's intact ego. In approximately 1,000 episodes in a private psychiatric setting, dissociative defensive maneuvers were rare (1 to 24 hours), and no lasting negative effect was observed. Interaction between nternal and external symbolization in sym-bolic resistance was used as a tool in the therapy of an adult female who had an alco-holic problem, depression, suicidal ideation, and, in general, deep hostility toward her-self and others. Dosage was 200 micrograms SD p.o.; 100 mg chlorpromazine was given -½ hours later as termination medication.

rkansas State Hospital
ittle Rock, Arkansas

30 Dundee, John W., Nicholl, Robert M., & Moore, James. **The influence of henothiazine premedication on methohexitone osage.** Anaesthesia, 18:41-45, 1963.

he action of various phenothiazines on the verage dose of a barbiturate, methohexitone, equired for prolonged body-surface opera-ions in which the barbiturate is adminis-ered intermittently in combination with a ixed concentration of nitrous oxide, is re-orted. The effect of pethidine and the lytic cocktail" (two parts pethidine and ne part each of promethazine and chlorpro-azine) are also presented. The phenothia-ines were given in combination with 0.6 mg tropine as premedication in healthy male ubjects. The phenothiazines were injected .m. 40 to 60 minutes before anesthesia; the ytic cocktail was injected i.v. 70 to 90 inutes before anesthesia. The analgesic r antanalgesic action of the phenothiazines ppears to be the important factor in deter-ining their effect on methohexitone re-uirements. Promethazine and pecazine, hich are antanalgesics, increase barbitu-ate requirements, but perphenazine and tri-lupromazine, which have only slight antan-lgesic action, cause an increase in barbi-urate requirement, which is followed by a arked reduction if the operation continues or longer than 30 minutes. The analgesic henothiazines, promazine and chlorpromazine, ause significant reduction in barbiturate need after 30 minutes of anesthesia. Pethi-dine and the lytic cocktail cause a striking reduction in barbiturate need. Results sug-gest that many phenothiazines show a bipha-sic response. When they exert an antanal-gesic action, there is an associated increase in barbiturate need; if this is followed by an analgesic action, they potentiate barbi-turate action.

Queen's University of Belfast
Northern Ireland

631 Brodie, Rosemary E. & Dow, Robert S. **Chlordiazepoxide in epilepsy.** North-west Medicine, 61(6):513-516, 1962.

Twenty-nine patients, 15 male and 14 female, with longstanding, incompletely controlled epilepsy, were treated with chlordiazepoxide in combination with from one to three other anticonvulsants. Diphenylhydantoin was used most commonly in combination with chlordiazepoxide. Patients were kept on chlordiazepoxide from 1 to 18 months, with an average of 9 months. Dosage ranged from 10 to 110 mg daily; most patients used 10 mg three to four times a day. Response to treatment was variable: 6 patients showed practical control, 13 showed a degree of temporary reduction of seizures, 5 showed no change in seizure pattern, and 5 were ad-versely affected. Primary side effects were drowsiness and ataxia; and increase in appetite was sometimes noted. Three case histories are given illustrating minimal im-provement, temporary practical control, and adverse effects with chlordiazepoxide ther-apy.

Good Samaritan Hospital
Portland, Oregon

632 Cline, William B., Jr. **Treatment of emotional disorders with amobarbital, diazepam, and psychotherapy.** Texas Journal of Medicine, 59:512-517, 1963.

Results of combined treatment with intrave-nous amobarbital, psychotherapy, and daily oral administration of diazepam were eval-uated in 84 office patients, 56 females and 28 males, ranging in age from 11 to 71 years. Emotional disorders treated included anxiety, depression, tension, schizophrenia, conversion reaction, postconcussion convul-sive disorder with instability, obsessive-compulsive reaction, and acute alcoholism. Amobarbital is given following the psychiat-ric interview. The average initial dose is 2.6 grains in sterile distilled water i.v. Subsequent doses are increased to 2.8, 3.0, 3.2 grains or more, depending on degree of

relaxation required. Injections are given at intervals of 5, 7, 10, 12, 14, 21, and 30 days. Oral doses of from 2 to 30 mg of diazepam are begun five days after the initial amobarbital injection; most patients receive the drug in 5 mg doses two or three times daily. Combined amobarbital and diazepam treatment continued for 5 days to 9 months, with an average of 3 months. Response was excellent in 30 cases, good in 34 cases, fair in 9 cases, and poor in 11 cases. Psychotherapy is greatly facilitated by this treatment method.

2471 Morgan Avenue
Corpus Christi, Texas

633 Hsu, John J., Braun, Robert A., Domino, Edward F., Lowinger, Paul, Schorer, Calvin, & Bruck, Morris. **Clinical evaluation of hydroxyphenamate in psychotic patients.** Diseases of the Nervous System, 24(12):1-2, 1963.

A group of 20 chronically disturbed psychotic female patients, 18 to 55 years old, were subjected to a 6-week, double-blind study. The group consisted of 18 schizophrenics and 2 patients with chronic organic brain disease. All had received phenothiazine drugs for at least 2 months prior to the study, except for one patient who had received chlordiazepoxide. All psychotropic drugs were discontinued, and a chlorpromazine placebo was given for 2 weeks. Daily dosage ranged from 800 to 3,200 mg. It was found that hydroxyphenamate did not improve the patients' behavior or symptomatology, as compared with phenothiazine. Given soon after chlorpromazine, hydroxyphenamate may have a synergistic or additive effect. Pharmacological activity of hydroxyphenamate is shown by more side effects, including drowsiness and ataxia, than its placebo.

Pontiac State Hospital
Pontiac, Michigan

634 Dobkin, Allen B., Robidoux, Henry J., & Israel, Jacob S. **Circulatory response to tilt with hydroxyzine, thiethylperazine maleate, SA 97, and perphenazine.** Anesthesia and Analgesia, 42(2):225-231, 1963.

The effects of i.v. administration of thiethylperazine maleate and hydroxyzine on circulation and on circulatory stress were compared with the effects of a potent antihistaminic, methyl homopiperazine dihydrochloride (SA-97), and a potent antiemetic, perphenazine, both of which are also potent sedatives. Tests were made in 10 healthy male subjects 20 to 30 years old, weighing 135 to 205 pounds (mean weight 168 pounds), at 1- to 3-day intervals, using hydroxyzine in 50- and 75-mg doses, thiethylperazine in 5- and 10-mg doses, SA-97 in 25- and 50-mg doses, and perphenazine in 5-mg doses. None of the drugs tested had any appreciable effect on the supine blood pressure, even when the subjects were tilted 60-degrees head-up. Although hydroxyzine (75 mg) and SA-97 (25 and 50 mg) retarded the pulse slightly, this probably was due to their sedative action. Most subjects exhibited drowsiness after hydroxyzine and perphenazine injections. Three subjects became drowsy after SA-97 (50 mg) and thiethylperazine (10 mg), but none showed this reaction to the lower dose of either drug. Restlessness persisting for several hours appeared in 8 subjects given perphenazine.

Upstate Medical Center
Syracuse, New York

635 Darling, Harry F. **A comparative study of diazepam and chlordiazepoxide in psychoneurotic patients.** Diseases of the Nervous System, 24(8):1-3, 1963.

The effects of diazepam and chlordiazepoxide, closely related drugs that relieve anxiety and tension, were compared and contrasted in ambulatory psychoneurotic patients. Two groups of 100 patients each, one group taking diazepam and the other group taking chlordiazepoxide, were treated for two months. Patients were of all ages. Median duration of illness and median age were less in patients receiving diazepam. Dosage ranged from 2.5 to 100 and 20 to 300 mg per day p.o. of diazepam and chlordiazepoxide, respectively. Based on pharmacological potency, 1 mg diazepam is equivalent to 2.5 mg chlordiazepoxide in effectiveness; in this study, the dosage ratio was 1:4. The two drugs were similar in action and results, and interchangeable in almost all cases. Side effects included slight drowsiness or ataxia, which were controlled by reducing dosage without impairing improvement. Ataxia was encountered less often with diazepam, and ptosis did not occur.

159 Swan Street
Methuen, Massachusetts

636 Chen, Calvin H. & Poim, Senta. **Carphenazine in the treatment of schizophrenia.** Current Therapeutic Research, 5(4):195-197, 1963.

The tranquilizer carphenazine maleate was tested in 71 chronic, regressed, schizophrenic patients, 55 female and 16 male, ranging in age from 22 to 70 years. Duration of illness ranged from 10 to 30 years, and symptoms consisted of delusions, hallucinations, mannerisms, seclusiveness, anxiety, hostility, and combativeness. Twenty-seven female and 8 male patients were given carphenazine, and 28 female and 8 male patients were given placebo. They were started on 12.5 mg t.i.d.; dosage was increased by the same amount at weekly intervals to a maximum of 75 mg t.i.d. Of those on carphenazine, 18 showed marked improvement, 13 showed moderate improvement, and 4 showed no change. The optimum dosage was 25 mg t.i.d. Signs of improvement were seen in from 1 week to 1 month. Side effects were observed in 8 patients treated with carphenazine, but in none of the placebo group. Extrapyramidal disturbances (rigidity and tremors) occurred in 5 patients. These were controlled by decreasing the dosage. After medication was discontinued, patients reverted to their original condition.

Northville State Hospital
Northville, Michigan

637 Stein, Sam I. **Treatment of hypertension in neuropsychiatric practice—— The clinical application of L-tryptophan.** Journal of Neuropsychiatry, 4:296-309, 1963.

A biochemical method for treating vascular hypertension is given, based on adjusting various phases of disturbed neural physiology. Treatment includes the administration in combination of specifically variable amounts of L-tryptophan, reserpine, pyridoxine, and a source of magnesium cation. Sixteen case histories are presented that describe results with various ranges of dosages of these four agents. Two combinations were found to be most practical: (1) a starting dose, or where a smaller amount of medication is indicated, consisting of 125.0 mg L-tryptophan, 0.1 mg reserpine, 2.5 mg pyridoxine hydrochloride, and 5.0 mg magnesium trisilicate; and (2) a dose to be used following initial treatment with the first combination, or where a stronger dose seemed indicated at the beginning of treatment, consisting of 125.0 mg L-tryptophan, 0.25 mg reserpine, 10.0 mg pyridoxine hydrochloride, and 20.0 mg magnesium trisilicate. Medication is, by tablet, administered orally one to six (usually four) times daily. Side effects are negligible, and treatment can be started before laboratory tests are run. The probable biochemical effects of each agent in the human being are discussed.

Bertram and Robert Stein Neuropsychiatric Research Program
4535 Oakton Street
Skokie, Illinois

638 Agin, Henry V. **Phenelzine in the treatment of depression.** American Journal of Psychiatry, 119:1173-1174, 1963.

In a group of 77 patients (36 women and 21 men, ranging in age from 19 to 72 years), the diagnoses were psychoneurotic depression in 49 patients, psychotic depression in 27, and postpartum depression in 1. Phenelzine sulfate was prescribed, the dosage being based on the severity of depression. The majority of the patients received initial and maintenance doses of 15 mg t.i.d. Physical and laboratory studies were performed before, during, and at the completion of the study. Approximately 82% of the patients responded to phenelzine therapy; and 70.1% obtained satisfactory results. The response was excellent in 69.4% of the patients with psychoneurotic depression, in 70.4% of those with psychotic depression, and in 1 patient with postpartum depression. The response to the drug was evident within 5 to 15 days, and it was most evident in the older age groups. The side effects of headache, insomnia, and constipation were mild and easily controlled. Mild orthostatic hypotension occurred in hypertensive patients, but was easily overcome by the use of methylphenidate.

Beth El Hospital
Brooklyn, New York

639 Lamb, Richard R. & Rivero, Augusto, S. **Propiomazine as a supplement to regional and general anesthesia for both prolonged and brief operations.** Anesthesia and Analgesia, 42:247-252, 1963.

Of 100 patients given propiomazine to reduce or eliminate basal anesthetic agents, 44 were male and 56 were female. The patients were 13 to 76 years old, with average age of 47 years; 69% were over 40 years of age. In this series, 5 to 30 mg of the compound was administered i.m. or i.v., and a second dose was necessary during the procedure for 26% of the patients, i.m. in 20 cases and i.v. in 6 cases. Anesthesia used in these procedures were spinal, continuous epidural, inhalant, caudal, brachial block, and thiopental alone. Results with the initial dose were excellent in 39%, satisfactory in 47%, and inadequate in 14%. With the use of propiomazine, the level of anesthesia could be maintained with much lower concentration of gas and a smaller

total amount of gas for the same operation and same length of time. Propiomazine made the patient more receptive to the analgesic action of meperidine or morphine. The reduction in blood pressure usually expected was by propiomazine. Side effects consisted of twitching and involuntary arm movements in two patients.

Mercer Hospital
Trenton, New Jersey

640 Delay, Jean, Deniker, P., & Conte, C. **Psychose de type schizophrénique associée à des troubles endocrino-métaboliques d'origine organique. (Schizophrenic psychosis associated with endocrine-metabolic disturbances of organic origin.)** Annales Médico Psychologiques, 1(2):327-331, 1962.

Diencephalic origin of certain symptoms of the schizophrenic series is suggested by a case combining schizophrenic evolution with polyendocrine manifestations. The patient, a 29-year old female, had birth trauma (apparently dead for 1 hour, subconjunctival hemorrhage, major cranial deformation, and alimentary difficulties for the first few weeks). At age 27, the patient showed atypical, progressive depression, accompanied by anxiety and withdrawal. Anomalies in the perceptive-motor tests indicated a psychoorganic origin. At age 29, the patient was treated with p.o. prochlorpromazine, the dosage being gradually increased to 100 mg daily. Anxiety and pseudophobic phenomena disappeared in 5 months of treatment. Since that time, she has been maintained on 20 to 30 mg prochlorpromazine daily, and appears stabilized in the residual state often observed in treatment of schizophrenics managed with neuroleptics.

(No address)

641 Witton, Kurt & Hermann, Harland T. **Clinical experiences with acetophenazine in the elderly psychotic.** Diseases of the Nervous System, 24:314-318, 1963.

Acetophenazine, the 2-acetyl derivative of perphenazine, was studied in a group of 41 elderly male psychotics of long standing who were not responsive to previous treatments. Optimal dose was found to vary between 30 and 60 mg daily in divided doses; in severely disturbed patients, an increase of up to 180 mg daily for short periods was found satisfactory. Of the 30 patients with functional psychosis, 12 showed great improvement, and 12 showed slight to moderate improvement. Four patients were rated unchanged, and two were worse. Of 11 patients diagnosed as having organic psychoses, 3 were rated greatly improved; 5 were slightly to moderately improved; and 3 were unchanged. Thus, 78% of the group showed measurable improvement. All tests were taken approximately 2, 6, 12, and 18 months after start of treatment. Clinical side effects were observed in a total of 16 patients. Five patients had a hypertensive response; 5 patients showed hypotension; 2 patients had convulsive seizures; and 1 patient had leukopenia without major clinical manifestations. None of the patients developed tremors or rigidity of major entity. Special attention was paid to "paradoxical" hypertensive pressure responses as described in five cases. Three cases that demonstrate the efficacy of treatment are presented. Acetophenazine is effective in suppression of psychotic ideation, and in improving alertness, mood, and affect.

Veterans Administration Hospital
Fort Meade, South Dakota

642 Rajotte, Paul & Denber, Herman C. B. **Long-term community follow-up of formerly hospitalized psychotic patients,** Journal of Nervous and Mental Disease, 136: 445-454, 1963.

The duration of remission of two groups of 50 schizophrenics receiving treatment were compared after a minimal followup of 2 years. In the experimental group, 32 patients received prochlorperazine (dosage range of 30 to 150 mg daily); 4 patients received thioperazine (dosage range of 10 to 150 mg daily); 6 patients received chlorpromazine (dosage range of 200 to 300 mg daily); 1 patient received haloperidol (3 mg daily); and 3 patients received imipramine (73 mg daily). Because of the small number of patients, no valid correlations can be established among relapse rate, a given drug, or dose. After 2 years, the relapse rate was 32% for the experimental group and 52% for the control group. The difference between means (87.02 weeks of remission for the control group and 71.68 weeks for the experimental group) was significant at the 0.05 level, but not at the 0.025 level, and variance was not significant at the 0.05 level. While chemotherapy appears to be the most important factor in preventing relapse, it must be viewed in the light of the patients' psychopathology. Thirty-eight of 43 patients could not conceive of how a drug might help them. Their acceptance of medication seemed to be based on the transference relationship. The most intensive treatment did not affect the duration of remission in those patients with cyclic relapses.

anhattan State Hospital
ard's Island, New York, New York

43 **Emylcamate in the treatment of psychoneurosis.** Practitioner, 190:524-526, 963.

mylcamate was administered to a group of 03 patients with mild, acute, and chronic sychoneurosis in order to determine whether ifferences of action could be demonstrated n relation to symptomatology. Female pa-ents outnumbered male by 3 to 1, and the aximum incidence was in the 31 to 50 age roup. The total number of patients in the ial fell progressively as it proceeded, e to patients' withdrawing from the trial r various reasons. The percentage of com-etely successful results improved from 25% 43%, as the trial progressed, to the end the fourth week. At the end of the urth week, 30% of the patients in this ial were obtaining partial relief of symp-ms. The results were further analyzed in lation to the sex and marital status of e patients, and rather better results were corded for the married female patients an for single female patients and males. higher incidence of side effects was re-rded with emylcamate than with previous medies, since only 69% of patients experi-ced no side effects with emylcamate. The mmonest side effect was drowsiness, occur-ng in 16%, followed by headache, vertigo, d disorientation. Treatment had to be itted in 4% of the patients because of ese side effects. It was concluded that ylcamate was an effective treatment for ute anxiety states.

o address)

44 Chu, Johnson & Fogel, Ernest J. **A preliminary study of 51 cases. Clinical valuation of the thymoleptic effect of anylcypromine.** Journal of the Indiana tate Medical Association, Winter Issue:40-42, 63.

e administration of 30 mg daily of tranyl-promine alone or in combination with sychopharmacological drugs, mostly tran-ilizers, produced marked to moderate erapeutic response in 37 (72.5%) of 51 spitalized patients with primary or secon-ry depressive symptoms. It seems particu-rly useful in patients who had shown mar-nal improvement and in those who had ached a plateau of improvement from other ug therapies. Most patients responded within 2 weeks, although some responded in 4 days, and others in 4 weeks. Side effects of hypotension, overstimulation, vertigo, and headache, while relatively frequent, were seldom severe enough to interfere with therapy. It is suggested, however, that tranylcypromine compares favorably with other monoamine oxidase inhibitors and appears to provide more rapid therapeutic effects.

Logansport State Hospital
Logansport, Indiana

645 Robin, A. A. **A retrospective controlled study of tranquillizers in long-stay patients.** Journal of Neurology, Neurosurgery, and Psychiatry, 26:262-264, 1963.

A study was conducted to examine the effect of tranquilizers on outcome, using controls, by a retrospective analysis of 276 matched pairs in each of which one patient was treated with tranquilizers. The tranquilized patients were treated with chlorpromazine (260), reserpine (81), pecazine (44), prochlorperazine (36), acetylpromazine (22), promazine (10), perphenazine (8), trifluoperazine (4), triflupromazine (4), and thiopropazate (3). Dosage was as follows: 45 patients received more than 300 mg chlorpromazine daily, the highest dose being 1,050 mg daily; 125 received 75 to 100 mg t.d.s., 55 received 50 mg t.d.s., and 35 only 75 mg daily. Twenty-nine patients received more than 3 mg reserpine daily, 72 patients received 3 mg, and 20 received less than 3 mg per day. Each tranquilized patient was matched with the untreated patient of the same sex, age in 10-year blocks, and diagnosis nearest to him in the index. Inspection of the overall results shows equal numbers discharged after a similar period of treatment from both the tranquilized group and the control group, even when the former have added to them all successes from the unmatched cases. Finally, when the patients discharged from drug and control groups are compared, they are shown to be similar in the distribution of diagnosis, length of stay before treatment, age, and sex, and the stability of their discharge is also similar in that 5 drug-treated patients of 25 discharged were readmitted as compared with 4 controls readmitted. Tranquilizers did not improve their chances of discharge from the hospital, accelerate discharge, affect their chance of readmission, or affect the death rate. (No side effects from the tranquilizers are reported.)

Runwell Hospital
Wickford, Essex

646 Boswell, John I., Prange, Arthur J., Jr., Abse, D. Wilfred, & Cochrane, Carl M. **Failure rate of tranquilizers as an index of drug effect.** Journal of New Drugs, 3:96-105, 1963.

A study was performed on 108 patients to determine the failure rate of tranquilizers as an index of drug effect. Reserpine (19 patients), chlorpromazine (24), powdered opium (29), and placebo (36) were administered on a double-blind basis. (No dose rates are given.) The discussions and arbitration method used in classifying cases by the physicians were felt to be optimum for obtaining valid results. Forty-six patients were suffering from schizophrenia, 25 were affective psychotics, 37 were nonpsychotics, and 31 had depressive symptoms. There were 34 male and 74 female patients. It was found that chlorpromazine and reserpine yield much higher success rates than opium and placebo in psychotic patients judged to be treatment successes or failures. In nonpsychotic patients, there was no statistically significant difference between the four substances. The failure rate in the double-blind test was 54% of 108 patients. The success rate increased from 46% to 88% when the physician prescribed the treatment of choice. No side effects of the drugs are given.

University of North Carolina
School of Medicine
Chapel Hill, North Carolina

647 Gross-Gorton, Virginia E. **Combined tranylcypromine-trifluoperazine therapy in newly admitted depressed patients.** American Journal of Psychiatry, 120:392-393, 1960.

Tranylcypromine was administered with trifluoperazine to 40 newly admitted depressed patients, 10 men and 30 women, ranging in age from 40 to 80 years. Eighteen patients were diagnosed as involutional psychotics, 9 as manic-depressives depressed phase, 5 as psychotic depressives, 6 as psychoneurotic depressives, and 2 as CBS with cerebral arteriosclerosis with depression. In women, tranylcypromine was initiated with 20 mg daily and was increased, according to need, to a maximum daily dosage of 50 mg; most patients responded to 30 mg. In men, dosage ranged from an initial 30 mg to 70 mg daily; the average dose was 40 mg. Trifluoperazine was given concomitantly to both women and men in doses of 2 mg b.i.d., and increased to a macimum of 10 mg daily. Hypotension, seen only among women, was the most common side effect observed. A 51-year-old woman developed a severe atypical reaction with extensive pyramidal tract involvement after receiving 20 mg of tranylcypromine and 10 mg of trifluoperazine for 6 days. Three patients, who inadvertently received one or two doses of tranylcypromine without trifluoperazine during the study, became agitated, anxious, or restless. No significant changes in blood counts or liver-function tests were observed. Twenty-four patients showed an excellent response and were discharged within 1 to 3 months after admission. Ten patients showed moderate improvement; 6 had not improved 6 months after admission.

Alaska Psychiatric Institute
Anchorage, Alaska

648 Collins, James H. **Combination therapy for depression and anxiety.** Psychosomatics, 4:290-292, 1963.

Eight men and 30 women, ranging in age from 21 to 64 (average age 41), were administered 10 mg tranylcypromine and 1 mg trifluoperazine bi.d. for an average of 2 months. All the patients had symptoms of depression and anxiety. In 21 of the patients, the emotional distress was precipitated by various organic disturbances. Side effects were reported by 10 patients, including insomnia, nervous tension, and a slight increase in parkinsonism. Of the 21 patients with organic disease, 18 (86%) showed a response ranging from good to excellent; of the 17 patients without organic disease, 15 (88%) showed good-to-excellent response.

67 Madison Avenue
Memphis 3, Tennessee

649 Appelbaum, Alfred. **An ophthalmoscopic study of patients under treatment with thioridazine.** Archives of Ophthalmology, 69:578-580, 1963.

An ophthalmoscopic study was conducted on 77 retarded patients with emotional disturbances and behavior and related problems under treatment with thioridazine. There were 49 males and 28 females in the study group. The average age of the patients was 18.61 years. The patients were given from 100 to 600 mg of thioridazine per day for a period varying from less than 1 month to 14 months. Six patients received 200 mg t.i.d.; 2 patients received 100 mg t.i.d.; 4 patients received 100 mg q.i.d.; 4 patients received 50 mg b.i.d.; and 29 patients received 50 mg t.i.d. A total of 63 of the 77 patients were found to have apparently normal fundi and no gross pathology elsewhere in the

cular structures. No pigmentary retinopathy was observed in any of the 77 patients. hioridazine has the advantage that it roduces a lower incidence of troublesome ide effects than some other phenothiazines.

'airview State Hospital
'osta Mesa, California

650 Lovshin, Leonard L. **Treatment of histaminic cephalalgia with methysergide (UML-491).** Diseases of the Nervous ystem, 24:120-124, 1963.

lethysergide was administered to 159 patients rith histaminic cephalalgia (cluster headche, Horton syndrome) over a period of 2-½ ears. Male patients outnumbered females 40 to 19; the patients' ages ranged from 12 o 73 years, the majority being between 30 nd 50 years old. The initial dose of ethysergide was 8 mg daily (2 mg q.i.d.); f well tolerated, this regimen was continued until the attacks were controlled. In ome instances, a maintenance dose of from to 8 mg daily was used for several months. he largest dose given was 16 mg daily. ausea, the most common side effect, could ften be prevented by ordering the tablet to e taken after a meal. Aching in the extremities was the next most bothersome side ffect. Minor and transient neurologic and sychic disturbances were noted. Of the 159 atients, 123 (77%) showed some improvement, nd marked improvement (excellent or good) as apparent in 110 (69%). The 36 patients ith a poor result included 5 with severe nxiety neurosis, 2 who were psychotic, 4 no were previously chronic alcoholics, 1 no displayed conversion hysteria, and 1 who as severely depressed. Thus, methysergide ppears to be the most successful agent yet eveloped for treatment of histaminic ephalalgia.

ne Cleveland Clinic Foundation
leveland, Ohio

51 Rickels, Karl, Ward, Clyde, & Snow, Laurence. **Nialamide and placebo in pressed psychiatric clinic patients. (A ntrolled double blind study.)** Diseases the Nervous System, 24:548-550, 1963.

controlled study was conducted on 44 neutics, mildly to moderately depressed, usg 100 mg capsules of nialamide and placebo. here were 11 male and 33 female patients nging from 30 to 73 years of age. Twenty-o patients completed at least 6 weeks, 3 tients dropped out after 2 weeks, and 10 tients did not return after the initial visit. Patients were assigned in random to either drug or placebo, and were switched after 4 weeks to the other agent. Each group of patients took 2 capsules each A.M. during the 1st week and 1 capsule each A.M. during the subsequent 3 weeks. In addition, patients received 100 mg hydroxyzine at bedtime for sleep and to combat possible increased agitation produced by nialamide. All patients were clinically evaluated before receiving drugs and every 2 weeks thereafter. All patients evaluated their symptoms themselves on a 64-Item Questionnaire. The doctor evaluated the patient by completing the Depression Questionnaire. In general, the physicians tended to rate the patients as more markedly improved than the patient himself did. The nialamide and placebo, in combination with the hydroxyzine, did not differ in their symptom-relieving effects.

University of Pennsylvania
Philadelphia, Pennsylvania

652 Kent, Edward A. & Weinsaft, Paul. **Treatment of depression in the aged with opipramol.** Journal of the American Geriatrics Society, 11(7):663-669, 1963.

Opipramol, an MAO inhibitor, was administered to 55 geriatric depressed patients (13 men and 42 women), 65 to 93 years of age. Most were ambulatory; all had some form of cardiovascular disease; and some had systemic disorders. Most of the depressive syndromes were severe being diagnosed as follows: acute brain syndrome (1) case), chronic brain syndrome (22 cases), psychoneurotic depression (12 cases), personality disorder (2 cases), situational adjustment of old age (17 cases), and manic-depressive depression (1 case). The initial dosage of opipramol was 75 mg p.o. daily. Dosage was increased in 13 cases to 150 mg daily. Duration of dosage varied from 2 weeks to 8 months, the usual time being 3 to 4 months. About half of the patients received small doses of tranquilizers to help control anxiety or agitation; drugs for systemic disease were given as required. Nineteen mild, transient side effects were noted in 29% of the patients, all being 70 to 84 years old. The side effects were agitation, tremor, immobile facies, euphoria, dizziness, drowsiness, weakness, and dyspnea with atrial fibrillation. An overall satisfactory clinical improvement in depressed mood, anxiety, agitation, hypochondria, and other symptoms, as well as improvement in general well-being, was observed in 90.9% of the 55 patients. Opipramol was found to be an effective, well tolerated, psychotropic agent for the

treatment of various types of depression in elderly patients.

The Brooklyn Hebrew Home and Hospital
for the Aged
Brooklyn, New York

653 Dean, Stanley R. **Prophylactic chemo-psychotherapy. (I. Failure of MAO inhibitors to prevent recurrent psychotic depressions.)** Diseases of the Nervous System, 24:178-179, 1963.

The present report concerns those patients who recovered after electroconvulsive therapy, and were then continued on isocarboxazid in the hope that the drug might at least prove to be a prophylactic against future depressive episodes. The series included 9 patients, 1 male and 8 female, treated as office outpatients. All were diagnosed as manic-depressive psychosis, depressed type, and severe in nature. After intervals of 3 to 24 months, five patients have remained symptom free. (No side effects.)

122 Forest Street
Stamford, Connecticut

654 Holst, Bent. **Sordinol i Neuroseterapien. (Sordinol and neurosis therapy.)** Ugeskrift for Laegar, 125:161-165, 1963.

The effects of chlorpenthixol were studied in a group of 16 female neurotic patients, 26 to 54 years, with an average age of 42. Prior to the study, the number of patients receiving the various medication was as follows: methaminodiazepozid (chlordiazepoxide) (4), amitryptilin (4), imipramine (4), chlorpromazine (3), perphenazine (3), chlorprothixene (2), meprobamate (2), captodiam (1), iproniazid (1), methylphenidate (1), and reserpine (1). Chlorpenthixol dosage was 25 mg b.i.d. for 8 days, followed by 10 mg b.i.d. for 9 days, and a maintenance dosage of 5 mg b.i.d. for 15 days. The twelve who were helped by the treatment consisted of neurotics as follows: 6 anxious, 3 depressive, 2 anancastic, and 1 hysteric. Three anxious neurotics and one anancastic neurotic showed no improvement. Side effects included drowsiness, dullness, dizziness, restlessness, difficulty of accommodation, tremor, edema, and rigidity. Two subjects were dropped from the study---one because of restlessness and one because of edema, a side effect previously unreported in connection with this drug. The edema disappeared a few days after chlorpenthixol dosage was reduced. Laboratory measurements included leucocyte count, blood pressure, pulse, and electroencephalography. No results were obtained with a group of 10 ambulatory patients (7 anxiety and 3 anancastic neurotics), because there was no observation of effects, and because of concurrence of side effects.

(No address)

655 Oswald, Ian, Berger, Ralph J., Jaramillo, R. A., Keddie, K. M. G., Olley, P. C., & Plunkett, G. B. **Melancholia and barbiturates: A controlled EEG, body and eye movement study of sleep.** British Journal of Psychiatry, 109:66-78, 1963.

Continuous nocturnal recording of EEG and eye movements was carried out on 6 patients, who had not previously received hypnotics, and on 6 sex and age matched controls. The patients were 52 to 67 years old; the controls were 49 to 59 years old. The patients were ill with typical melancholia. Each patient received 400 mg of heptabarbitone on 2 nights and dummy tablets on 2 nights. All recordings were analyzed without knowing whether the record was that of a patient or of a control. Findings include the following: (1) Patients spent significantly more of the night awake, although times of awakening were not related to the recurrence of rapid eye-movement periods. (2) Heptabarbitone greatly decreased the duration of rapid eye-movement (dreaming) periods and also the frequency of eye movements within those periods. (3) Heptabarbitone decreased time awake, especially in patients in the early hours of the morning, and decreased frequency of shifts of sleep depth and frequency of body movement. (4) The EEG discriminated far better than body motility, which is subject to large individual variations. (5) Body motility decreased according to traditional EEG stages of sleep in association with traditional deep sleep.

University of Edinburgh
Edinburgh, Scotland

656 Waites, Lucius & Keele, Doman K. **Fluphenazine in management of disturbed mentally retarded children.** Diseases of the Nervous System, 24(2):113-114, 1963.

A study was made of the use of fluphenazine in the management of disturbed mentally retarded children with serious behavioral disorders. The series included 24 males and 4 females varying in age from 5 to 34 years, 15 of the 28 patients being between 5 and 10 years old. Fluphenazine dihydrochloride was administered orally to each of the patients in the series, either as a tablet

ontaining 1 mg or 2.5 mg of the drug, or
s an elixir supplying 0.5 mg in each cc.
osage ranged from 0.25 mg b.i.d. to 5 mg
.i.d., and the duration of treatment vari-
l from 2 weeks to 10 months in the indivi-
ual cases. The results that fluphenazine
s a useful and effective therapeutic adju-
ant in the management of some mentally re-
arded patients with severe behavioral dis-
rders. Hyperkinesis subsided, and re-
ractory and unruly behavior was brought un-
er practical control in 18 of the 28 pa-
ients. The reactions of generalized ex-
rapyramidal signs and of oculogyric crises
hat developed in 4 of the 28 patients were
isturbing but nonlimiting in the use of
luphenazine, because in every case, these
ide effects were reversible and disappear-
l soon after the medication was discontin-
ed.

niversity of Oklahoma Medical Center
klahoma City, Oklahoma

57 Barnett, Robert V. **Phenothiazine derivatives: An adjunct to obstetric analgesia with special reference to propiomazine.** Southern Medical Journal, 56:543-46, 1963.

his study was initiated to evaluate com-
aratively two phenothiazines (promazine
nd promethazine) commonly used to augment
nalgesia. Also, a new derivative, propio-
zine, was evaluated. A total of 396 pa-
ients was included in the study. Initial-
, four groups of patients were establish-
l, receiving in rotation analgesic com-
inations of drugs, in a double-blind
rrangement. The combinations consisted of
romethazine (25 mg), meperidine HCl (75 mg),
nd scopolamine (0.4 mg); promazine (25 mg),
peridine HCl (75 mg), and scopolamine
.4 mg); propiomazine (20 mg), meperidine
l (75 mg), and scopolamine (0.4 mg);
opiomazine (20 to 60 mg), meperidine HCl
0-75-100 mg), scopolamine (0.4 mg); and
e control meperidine HCl (75 mg) and
copolamine (0.4 mg). All drugs studied
emonstrated effectiveness in producing im-
oved maternal analgesia. The impression
s that propiomazine is especially adaptable
intravenous use and is completely com-
atible with conduction anesthesia. No ill
ffects upon the fetus were observed, nor
ere there significant fluctuations in blood
ressure or changes in course of labor. The
ncidence of nausea and vomiting was very
gh in all groups.

edical College of Alabama
rmingham, Alabama

658 Fisher, G. W., Murray, F., Walley, M. R., & Kiloh, L. G. **A controlled trial of imipramine in the treatment of nocturnal enuresis in mentally subnormal patients.** American Journal of Mental Deficiency, 67:536-538, 1963.

A trial was made of the effectiveness of imipramine in the treatment of nocturnal enuresis in mentally subnormal patients. In a double-blind 12-week study, imipramine and placebo were administered to 21 male and 13 female hospitalized patients, 7 to 67 years old, with diagnoses of mentally subnormal, severely subnormal, and severely subnormal epileptics. The drug, dosage 25 to 50 mg, was administered at 8:00 P.M. With the exception of the epileptics, the patients showed only slightly less frequent enuretic episodes than when on placebo. (No side effects mentioned.) In the dosage employed, imipramine was ineffective.

Prudhoe-on-Tyne
Northumberland, England

659 Montilla, Eduardo, Frederik, Willem S., & Cass, Leo J. **Analgesic effect of methotrimeprazine and morphine. A clinical comparison.** Archives of Internal Medicine, 111:725-728, 1963.

In a double-blind study of 105 hospitalized patients, a single 15-mg dose of methotrimeprazine hydrochloride provided analgesia comparable in degree to a 10-mg dose of morphine sulfate. The group of patients consisted of 88 male and 17 female, 24 to 86 years old, with a weight range of 92 to 206 pounds. The painful conditions requiring analgesics were postoperative pain, herpes zoster, cancer, osteoarthritis, coronary occlusion, fractures, neuritis, pleurisy, and various others. A single subcutaneous injection of two coded drugs was given at random to each patient (morphine to 44 and methotrimeprazine to 61). The patients given methotrimeprazine had a greater average amount of pain before administration than those given morphine, but they had almost identical degree of pain relief during the following 4 hours. The side effects of methotrimeprazine observed or volunteered by the patients were drowsiness (42%), vertigo, excitement, and constipation. A 3-month study of tolerance potentiality in 25 patients showed no dependence and no toxic manifestations.

San Jorge Hospital
Santurce, Puerto Rico

660 Stetson, John B. & Jessup, Gretchen V. S. **Oral premedication in children. Attempts to use Largon.** Anesthesia and Analgesia, 42(1):97–108, 1963.

An attempt to find the propiomazine hydrochloride dosage for surgical oral premedication of children resulted in doubts that oral propiomazine will have much use in providing nighttime, surgical, or obstetric sedation. A triple-blind study of children (mean age 6 years) was conducted, using 2 mg per pound propiomazine, 1 mg per pound meperidine hydrochloride, and 25 mg per pound chloral hydrate, each in combination with 0.025 mg per pound atropine. Meperidine gave light sedation and apparent good humor; more obvious sedation was obtained with chloral hydrate; and propiomazine produced light, irregular, or fitful sedation, without relief of anxiety. In a small-series study of young adults, propiomazine produced agitated sleepiness, generally without euphoria, at a dose level that had only slight effect in children. A 4-year-old boy weighing 39 pounds accidently received an overdose of 312 mg oral propiomazine and 3.9 mg oral atropine. He became sleepy, lacked coordination, his pulse increased, and an atropine flush appeared on the skin. The flush disappeared after approximately 3 hours (following surgery), and 8.5 hours after administration he began to hallucinate. He was discharged after 30 hours.

Harvard Medical School
Boston, Massachusetts

661 Payne, R. W., Friedlander, D., Laverty, S. G., & Haden, P. **Overinclusive thought disorder in chronic schizophrenics and its response to "Proketazine".** British Journal of Psychiatry, 109:523–530, 1963.

Judged by ward behavior and tests of overinclusive thinking, chronic schizophrenics are relatively unaffected by the high-potency phenothiazine derivative a-methylmetatyrosine. A double-blind study was conducted of 40 chronic schizophrenic ward patients, all receiving maintenance doses of drugs, mostly phenothiazines. All medication was stopped for 6 weeks. During this period, 11 were dropped because of regression, and the 29 remaining subjects were given the Benjamin Proverbs Test and the Goldstein—Scheerer Object Sorting Test. One group of 9 men and 6 women was given 25 mg a-methylmetatyrosine t.i.d. for 1 week, followed by 50 mg t.i.d. for 5 weeks. The remaining 8 men and 6 women were given placebo. After the 6-week period, all were retested with the object sorting test, and Payne's Object Classification Test was given. Ward behavior also was evaluated. The results of the tests show that a-methylmetatyrosine has no significant effect on patient improvement.

Queen's University
Kingston, Ontario, Canada

662 Whitwam, J. G., Moreton, T., & Norman, J. **Clinical signs with modified electroconvulsive therapy.** British Journal of Psychiatry, 109:399–403, 1963.

A modified electroconvulsive therapy technique that uses atropine pretreatment is described. The effects of 0.6 to 3.0 mg atropine s.c. and i.v., and of methohexital sodium and succinylcholine bromide on movement of skeletal musculature, respiration, eyelash reflex, and pupillary reactions are discussed on the basis of 170 observations of patients in 1961 and 1962. Cessation of fasciculation in the feet is useful in determining the time of optimum relaxation. In this, dilution of the succinylcholine bromide (0.5 mg/kg) to at least 2 ml effects good control of skeletal-muscle activity. The effectiveness of shock in producing convulsion is indicated by obliteration of the pupillary light reflex. Pupillary spasms during the modified clonic phase are slowed, and may be abolished by an i.v. administration of 1 to 3 mg atropine immediately before electrical stimulation. All the patients received long-term antidepressant therapy, consisting of imipramine, phenelzine, or tranylcypromine, plus nightly barbiturate or dichloralphenazone, and some received tranquilizers (trifluoperazine or chlordiazepoxide). Tranylcypromine was discontinued during the early part of the study.

General Infirmary at Leeds
Leeds, England

663 Baugh, James E. **Clinical and laboratory study of trichlormethiazide and reserpine in 52 patients with hypertension.** Angiology, 14:34–39, 1963.

A study was conducted with a group of 22 men and 30 women, 38 to 88 years old. All patients had moderate or severe hypertension; 9 had one or more cerebrovascular accidents; others had subacute glomerulonephritis, arteriosclerosis, arthritis, cancer, or diabetes; and many were overweight. Patients were divided into two groups, according to the duration of treatment. Both groups were given 6 to 12 mg of trichlormethiazide with 0.3 mg reserpine daily for 4 to 56 days, with a mean average of 9 days for group 1 and

f 32 days for group 2. Moderate or con-
iderable reduction in blood pressure (mean
verage 33/16 mm mercury) was recorded in all
atients. All but 6 (who received short
reatment) lost weight; the mean average was
.2 pounds. Edema in seven patients dis-
ppeared during treatment. Twelve reported
ignificant diuresis, although 43 of the
roup previously had only fair results with
ne or more diuretics. Of the 21 clinical
ide effects reported by 18 patients (34%),
nly pruritic rash could be attributed to
he compound; this disappeared when therapy
as discontinued. Changes in serum electro-
ytes, serum carbon dioxide, nonprotein
itrogen, urinary sugar or albumin, and
lood chemistry were very slight, and not
ttributable to therapy. It is concluded
hat 6 to 8 mg is an appropriate daily dose
f trichlormethiazide, and that 0.3 mg of
eserpine daily provides sufficient anti-
ypertensive activity when used with a suit-
ble diuretic agent.

37 West Hancock Street
illedgeville, Georgia

64 Mukasa, Hiroshi & Inanaga, Kazutoyo. **Study on the correlation between clin-
cal and physiological responses to chlor-
romazine.** Kurume Medical Journal, 10(1):
1-28, 1963.

lose relation was found between clinical
nprovement and the pattern of frequency
urves in EEG and minor tremor. Control EEG
nd minor tremor recordings were made more
an 1 week after discontinuation of vari-
us drugs of 10 male and 2 female hospital-
zed schizophrenics, selected at random.
ne EEG showed 6 cases with alpha dominant
ttern, 4 cases without dominant peak, and
cases with a peak in the theta band. The
ve analyzer used was modified to divide
e 6 to 13 cycle per second frequency range
to seven bands to analyze the alpha fre-
ency in detail. Chlorpromazine was given
dosage of 100 mg per day for 1 week, and
creased by 100 mg per day every week. The
ual dosage was between 200 and 600 mg per
y. The EEG and minor tremor recordings
re made 1 week after administration of
lorpromazine, and weekly thereafter, for 2
6 weeks. Overall comparison of the fre-
ency curves of both EEG and minor tremor
owed that EEG frequency curves in the
oup with an atypical initial pattern re-
rkably improved with chlorpromazine treat-
nt, whereas there were diverse unfavorable
anges in the group with a rather typical
itial pattern. The same tendencies were
served in the minor tremor pattern. (No
xic or side effects mentioned.)

Kurume University School of Medicine
Kurume shi, Japan

665 Treptow, Keith R., Affleck, D. Craig, Roehl, C. Allen, & Soelling, Warner M. **Nylidrin hydrochloride in senile arteriosclerosis.** Archives of Neurology, 9(2):142-146, 1963.

In a double-blind study, 20 hospitalized senile patients (12 men and 8 women), with a primary diagnosis of chronic brain syndrome associated with arteriosclerosis, were divided into two groups matched on age, sex, hospital adjustment, and performance on psychological tests. The mean age of the drug group was 79.1 ± 7.0 and that of the placebo group was 78.4 ± 8.7. Evaluation consisted of psychological tests and hospital adjustment tests at 8 and 14 weeks while on the drug, as well as rerating of behavior at 2-week intervals. Nylidrin hydrochloride, a synthetic vasodilator chemically related to epinephrine and ephedrine, was initially given in a dosage of 18 mg (6 mg tablet t.i.d.); it was increased, at intervals of several days, to 72 mg (three 6 mg tablets q.i.d.) at the end of 5 weeks. There were no complaints of ill effects, and no pathological results were noted. Seven patients in each group continued to receive tranquilizers during the study. Results showed that, relative to the placebo group, the drug group approached significant improvement on the Digit Span and Black Design Tests, but there was a significant decline in the hospital adjustment scale ratings.

University of Nebraska College of Medicine
Omaha, Nebraska

666 Lapolla, Anthony. **Possible role of potassium in production of parkinsonian-like symptoms with use of tranquilizers: Clinical observation.** Clinical Medicine, 70:533-536, 1963.

Thirteen patients, physically normal and with normal ECG, were given (p.o. or i.m.) a tranquilizer that was known to produce profound parkinsonian-like symptoms when administered in high doses for long periods. After the severe symptoms had persisted for 10 days, all patients were given an anti-parkinsonian drug. If relief occurred, the tranquilizer dosage was increased until the patient no longer responded to the anti-parkinsonian drug. Blood studies done at this time were still normal. The clinical impression suggested a potassium deficiency as evidenced by T-wave changes in the ECG of five patients. Potassium chloride (5 grain)

tablets and fruit juices were given, along with the tranquilizer, t.i.d. to the five patients. Within 3 days, the parkinsonian-like symptoms showed clinical decrease, and in 7 to 10 days, the symptoms had almost or completely subsided. The ECG showed normal T-waves and normal tracings in all subjects. Repetition of this study with another group of patients duplicated these findings.

(No address)

667 Farb, Harry H. **Intravenous diazepam as pre-interview medication.** Diseases of the Nervous System, 24:233-236, 1963

Diazepam, a derivative of chlordiazepoxide, was given in private psychiatric practice to 21 females and 13 males, 21 to 62 years old, to reduce anxiety, depression, phobias, and agitation during the psychotherapy sessions. The disorders in this group were generally severe and refractory. The drug was administered i.v. in doses of 10 to 30 mg just prior to the first three interviews. All patients received concurrent therapy. Thirty-one patients were given diazepam p.o. in doses of from 6 to 75 mg. Three of these patients also received 5 mg p.o. of dexedrine daily to elevate depressed moods. Six patients were given 20 mg methamphetamine hydrochloride i.v. to induce talkativeness. Ten patients (8 males and 2 females) reported moderate pain at the site of the injection. All but 2 patients showed marked or moderate response to treatment. There was remission of all target symptoms, with the exception of confabulation displayed by one patient. The remission resulted in improved patient-therapist relations and greater progress in psychotherapy. Onset of the effect of diazepam was immediate. Slight vertigo, lasting for several hours, occurred in all but one patient, and nausea occurred in one patient. There was striking lack of sedation, and all patients remained alert throughout the interviews. Side effects did not adversely affect symptomatic response.

(No address)

668 Blumberg, Arnold G., Klein, Donald F., & Pollack, Max. **Effects of chlorpromazine and imipramine on systolic blood pressure in psychiatric patients: Relationships to age, diagnosis and initial blood pressure.** Journal of Psychiatric Research, 2:51-60, 1963.

A group of 144 hospitalized patients was studied in a double-blind procedure; 43 received placebo; 52 received imipramine (75 mg per day); and 49 received chlorpromazine (300 to 1,200 mg per day) plus procyclidine (3.75 to 15 mg per day) to prevent induced parkinsonism. Of the 114 patients who completed the blood-pressure study, 67 were diagnosed as schizophrenics, 39 as depressive syndromes, and 8 as character disorders. The reliability of the test procedure was estimated by product-moment correlations of the pre-drug and on-drug systolic blood-pressure measurements. The drugs were compared with placebo as to the mean change and variability of change. A common regression coefficient was utilized for the entire sample. At the end of the 7th week, no changes in mean resting blood pressure were found in connection with chlorpromazine. Imipramine induced a significant increase in blood pressure in the schizophrenic group relative to the placebo group. Both placebo and imipramine produced small decreases in systolic blood pressure in the depressed patients. The rise in systolic blood pressure in the schizophrenic group on imipramine and the absence of this effect in the depressed group cannot be ascribed entirely to age differences. Changes in systolic pressure with imipramine and with chlorpromazine were significantly related to diagnosis, age, and initial level. (No side effects or toxicity mentioned.)

Hillside Hospital
Glen Oaks, Long Island, New York

669 Bartholomew, Allen A. **An assessment of the therapeutic efficacy of "Trepidone".** Medical Journal of Australia, 50: 150-151, 1963.

A small pilot investigation, using the double-blind technique, was used to evaluate the tranquilizer mephenozalone. A group of 24 neurotics (mixed chronic neurotic states) and a group of 40 alcoholics were divided into 12 pairs and into 20 pairs, respectively, matched in terms of age, sex, predominant symptom, and duration of condition. All patients were given placebo for the first week, followed by either drug or placebo for 3 weeks. The drug dose was 1,600 mg per day (1 tablet q.i.d.). No other drug was prescribed during this period, although supportive psychotherapy continued. In the neurotic group, 5 of the 12 patients receiving the drug improved, in contrast to 7 patients taking placebo. Nine alcoholics improved in both the drug and the placebo groups. Side effects were mild and nonspecific, and were distributed almost equally between the drug and placebo groups. One patient with chronic anxiety complained of nausea, vomiting, and severe headache. These

complaints disappeared when the patient was changed to chlordiazepoxide. The results indicate that mephenozalone in the dosage used is of no real value in treating neurotics or alcoholics.

Alexandra Clinic
Department of Mental Hygiene
Victoria, Australia

670 Honigfeld, Gilbert. **Follow-up of depressed patients treated in a multihospital drug study. II. Psychiatric evaluations.** Diseases of the Nervous System, 24:160-161, 1963.

A followup study of 72 male depressed patients was conducted for 1 year. The evaluation schedule for this project called for five psychiatric ratings: at pretreatment and at 3, 12, 20, and 52 weeks after the start of the double-blind study of chemotherapy in depression. The drugs used were dextroamphetamine-amobarbital, isocarboxazid, imipramine, or placebo. Independent ratings were made on the Inpatient Multidimensional Psychiatric Scale, based on a joint interview by a psychiatrist and a psychologist. The results showed reduction and amelioration in the following areas: agitated depression; a special depression scale; excitement; hostile belligerency; withdrawal; and conceptual disorganization. The two depression scales showed pronounced and rapid improvement from pretreatment to 12 weeks. After the 12-week or dropout rating, no further improvement in these areas was seen. In the other four areas, modest improvement continued steadily through the year, with the most significant gains being made in the first 20 weeks.

Veterans Administration
Central Neuropsychiatric Research Laboratory
Perry Point, Maryland

671 Henne, Tonnel, M., & Henne, S. **Chimiorésistance généralisée d'une schizophrène lobotomisée. (Generalized chemical resistance of a lobotomized schizophrenic.)** Annales Médico-Psychologiques, 1:145-147, 1962.

The clinical case of a lobotomized female schizophrenic is described, in which lobotomy is suspected as the cause of general chemical resistance to neuroleptics. The patient was admitted in 1947 at age 14. Electroshock was tried, and following a relapse, prefrontal lobotomy was performed in 1950, producing temporary psychic improvement. The following therapies were tried in succession between 1950 and 1960: a series of electroshock treatments plus chlorpromazine injections and sodium amytal; 10 sessions of malarial fever; 150 to 375 mg chlorpromazine p.o. plus 20 electroshock treatments; chlorpromazine with 81 insulin comas; up to 1 g chlorpromazine p.o. and up to 12 mg reserpine; a cocktail of 200 mg chlorpromazine, 200 mg promethazine and 8 mg reserpine; 100 to 500 mg levomepromazine; 1 to 40 tablets prochlorpemazine plus chlorpromazine (decreasing from 400 to 200 mg); 100 to 200 mg levomepromazine, to which was added up to 20 mg reserpine plus antiparkinsonian drugs; polybromureic solution; pneumoshock; the cessation of neuroleptics for 1 year; 4 to 12 tablets alimemazine; 5 to 15 mg thioproperazine; 200 mg chlorpromazine plus 95 mg thioproperazine; and haloperidol and thioproperazine. Each drug treatment produced temporary sedation, followed by resistance to high doses and by continued violent behavior.

(No address)

672 DiFrancesco, Armand. **Diazepam, a new tranquilizer.** American Journal of Psychiatry, 119:989-990, 1963.

A group of 26 patients of both sexes, age 7 to 78, all showing moderate to severe overt anxiety and tension, was chosen for a 4-month double-blind study of diazepam. The diagnoses of the patients were as follows: chronic anxiety neuroses (7), obsessive-compulsive neuroses (3), anxiety hysteria neurosis (1), axhizoid personality (1), schizophrenia (12), passive--aggressive personality disorder (1), and adjustment reaction of childhood (1). Onset and duration of mental illness and the adjustment of the patients were extremely varied. All patients had received some psychiatric treatment, including electroconvulsive therapy, tranquilizers, antidepressants, and psychotherapy. The patients were given either diazepam or placebo. Medication was switched after 2 weeks and after 4 weeks. At the end of 6 weeks, all the patients were placed on diazepam for 1 to 3 months. Dosage started at 2-$\frac{1}{2}$ to 5 mg t.i.d., and was increased as necessary, with 40 mg as the maximum daily dosage given. Supportive psychotherapy was also given. Results showed definite reduction in anxiety and tension when diazepam was taken. Symptoms usually returned with the switch to placebo. At the end of the study, 5 patients showed marked improvement, 17 were moderately improved, 2 showed mild reduction of symptoms, and there was no change in 2 patients. Side effects, consisting of chiefly mild drowsiness, hypotension, and nausea, occurred in approximately 25% of the patients, and were easily controlled. No serious toxic effects were noted clinically.

Monsignor Carr Institute
Buffalo, New York

673 Kennedy, R. E. & Miller, J. J. Amitriptyline-perphenazine in the treatment of schizophrenia. American Journal of Psychiatry, 119:1092-1093, 1963.

In a continuing study, amitriptyline-perphenazine treatment is compared with previous methods of managing schizophrenic cases. One thousand patients in various diagnostic categories have been treated with these drugs at the Rollman Psychiatric Institute. The monoamine oxidase inhibitors were replaced by amitriptyline in combination with perphenazine in May 1961. By December 1961, satisfactory remissions increased to 84%, but 30% received electroconvulsive therapy in addition to the drugs, and by June 1962, remissions increased to 88%, and only 11% were given electroconvulsive therapy. With sufficiently high doses, patients began to sleep well, which appears to be the pivotal factor in recovery. Some patients report vivid dreaming with amitriptyline-perphenazine treatment, but not with barbiturates. Sedatives no longer need be given, and may be contraindicated. The 24-hour dose of amitriptyline was usually 200 mg, and that of perphenazine 64 mg or more. Benztropine in 0.5 mg to 1.0 mg doses was added to prevent drug parkinsonism.

Rollman Psychiatric Institute
Cincinnati, Ohio

674 Sutnick, Alton I., Fewell, J. William, & Soloff, Louis A. **Clinical observations on the antihypertensive effect of pargyline hydrochloride.** American Journal of the Medical Sciences, 245:166-170, 1963.

Pargyline hydrochloride, a powerful monoamine oxidase inhibitor, is an effective, but primarily orthostatic, hypertensive agent. A double-blind, crossover technique with placebo was used in the treatment with oral pargyline hydrochloride of 14 ambulatory patients, 10 women and 4 men, 26 to 70 years old, all having essential hypertension, except for 1 case of chronic glomerulonephritis. All antihypertensive therapy was stopped at least 2 weeks before the study. The initial dosage of 12.5 to 25 mg per day was increased by 25 mg daily until an adequate hypotensive effect was maintained for 4 weeks, or until a maximum dose of 200 mg per day (8 tablets) produced no effect after 4 to 8 weeks. Results showed a drop in blood pressure in 11 (79%), and a distinct, though lesser, drop in supine blood pressure in 5 patients. One patient developed disabling orthostatic hypotension. Some patients responded to as little as 57.5 mg per day, and the effect of a single dose may last 10 days. Five patients gained weight, and nocturia occurred in 3 patients. Other complaints included nervousness, transient dryness of the mouth, and constipation. The one case of leukopenia that developed appeared to be cyclic neutropenia, and thus was not a manifestation of drug toxicity.

Temple University School of Medicine
Philadelphia, Pennsylvania

See also: 570, 586, 590, 595, 676, 689, 697, 745, 755, 771, 781

575 Espir, M. L. E. & Mitchell, Logan. **Tranylcypromine and intracranial hemorrhage.** (Letter) Lancet, 2(7308):639, 1963.

Lumbar puncture is necessary to exclude or establish the diagnosis of subarachnoid hemorrhage in a patient who has severe headache and/or meningism while receiving tranylcypromine or some other MAO inhibitor. A woman of 65, who apparently had been taking "Tuinal" grain 9 each night for years, was prescribed tranylcypromine 10 mg and trifluoperazine 1 mg t.i.d. for agitated depression. After the 13th tablet, she developed a severe headache. She had not eaten any cheese, nor had she taken dexamphetamine. The drug was stopped, and the headache disappeared. However, in 48 hours the headache returned, was more severe, and was accompanied by vomiting. The patient was hospitalized with meningism. Her temperature was 100° F; her blood pressure was 130/70 mm Hg; and lumbar puncture showed heavily bloodstained fluid under 120 mm pressure, with xanthochromic supernatant fluid. Four days later, the patient was still very ill, and an intracranial bruit was heard over the right orbit and the right side of her neck. The bruit disappeared after 10 days. Bilateral carotid arteriography showed no definite abnormality, and she recovered completely.

(No address)

576 Kane, Francis J., Jr. & Taylor, Terry W. **A toxic reaction to combined Elavil—Librium therapy.** American Journal of Psychiatry, 119:1179-1180, 1963.

Acute brain syndrome with evidence of cerebellar dysfunction following ingestion of a combination of librium and amitriptyline is reported in a 48-year-old man suffering from acute depression. The patient took 40 mg of librium and 150 mg of amitriptyline daily. He became forgetful, confused, spoke with slurred speech, and seemed uncoordinated. Motor coordination was considerably impaired. Since librium is known to cause ataxia, motor-coordination impairment may be an exaggeration of this known side effect. The use of amitriptyline in combination with librium may have caused this exaggerated response.

University of North Carolina
Chapel Hill, North Carolina

677 Barraclough, M. A. & Sharpey-Schafer, E. P. **Hypotension from absent circulatory reflexes. Effects of alcohol, barbiturates, psychotherapeutic drugs, and other mechanisms.** Lancet, Spring Issue:1121-1126, 1963.

A considerable number of conditions are shown to cause loss of circulatory reflexes and hypotension. Alcoholic and diabetic neuritis or poisoning by barbiturates or drugs used in psychotherapy are common causes; porphyria and neuritis from carcinoma are rare causes and present difficulties in diagnosis. Cerebrovascular accidents also cause acute interruption of reflex pathways. Ten cases of acute loss of circulatory reflexes and 19 cases of chronic loss were studied. Acute loss of circulatory reflex was found in alcoholic intoxication, barbiturate poisoning, and overdose of psychotherapeutic drugs (meprobamate, phenothiazine, and desipramine). The mechanism of hypotension in circulations with loss of reflexes is explained, and its treatment is determined by the simple relation existing between stroke output and arterial blood pressure. Treatment was tried, using several venoconstrictors (adrenaline, noradrenaline, 5-hydroxytryptamine, and histamine), but correct dosage of these agents is difficult to achieve. Treatment with these venoconstrictors is inferior to simple blood-volume increase with a plasma expander.

St Thomas's Hospital Medical School
London, England

678 **Retinotoxic drugs.** (Editorial) Archives of Ophthalmology, 69:545-546, 1963.

Thioridazine in exceptionally high doses (600 to 2,000 mg) and 3-chloro-10,2--(N-methylpiperidyl-2")-ethyl-phenothiazine

(NP 207, 800 mg per day) are retinotoxic. Retinal effects include night blindness, diffuse narrowing of retinal arteries, early effect on central vision, and pigmentation occurring in large clumps rather than in bone corpuscle aggregates. Symptoms are partially reversible on discontinuation of drugs. The quinoline drugs, used to treat rheumatoid arthritis and lupus crythematosus (especially chloroquine and hydroxychloroquine), are also retinotoxic. Retinal involvement has occurred with doses that do not exceed therapeutic amounts (300 mg per day) when the drugs were used over a period of years. Symptoms are loss of central vision, granular pigmentation of the macula, constriction of arteries, and ring scotomas. Visual loss is irreversible. Dithizone causes acute neurosis of the retina in dogs by attacking the tapetum lucidum. Human beings have no comparable tapetum, so dithizone would not be expected to be as selectively toxic to human eyes.

(No address)

679 Kasanen, Antero & Valleala, Pentti. **Electroencephalographic findings in chronic phenacetin abusers.** Acta Medica Scandinavica, 173(1):35–40, 1963.

An electroencephalographic record was taken from 16 patients of the medical department who had consumed an average of about 2 kg of phenacetin. The patients' mean age was about 30 years, and they were all under 40. Two had mild azotemia, and the others had only impaired ability to concentrate; four had a history of migraine. A pathological electroencephalogram was obtained from 11 patients. The most typical EEG change was intermittent rhythmical slow activity in the frontal and parietal regions. In severe cases, the changes were generalized, and normal alpha activity was completely absent. An abnormal flicker reaction was established in seven cases. This reaction was epileptiform in three patients. A followup EEG was obtained after withdrawal from phenacetin from two patients whose clinical diagnosis had been hypophyseal insufficiency. The changes had become normal or diminished clearly in 9 and 11 months. The authors regard the changes as associated with long-term phenacetin abuse and correlate them with the cerebral symptoms demonstrated in the patients. (Author abstract)

University Hospital Medical Clinic
Turku, Finland

680 Groden, Bernard M. **Parkinsonism occurring with methyldopa treatment.** British Medical Journal, (5336):1001, 1963.

A case of parkinsonism induced by methyldopa is reported in a 57-year-old man suffering from hypertension. Previous to methyldopa treatment, the patient had developed parkinsonism from taking reserpine. The symptoms subsided and disappeared when reserpine was withdrawn. He remained hypertensive, however, and was stabilized on 250 mg methyldopa q.i.d. Four weeks later, there was slight evidence of a return of parkinsonism, which in the ensuing 2 weeks became more marked. No change was reported or seen in the patient's condition until methyldopa was withdrawn, when both subjective improvement was noted along with disappearance of limb stiffness, return of facial expression, and improvement in mobility.

Glasgow Royal Infirmary
Glasgow, Scotland

681 Elson, Abraham & Domino, Edward F. **Dextro propoxyphene addiction.** Journal of the American Medical Association, 183(6):482–485, 1963.

A case of dextro propoxyphene hydrochloride addiction is reported in a 28-year-old man with a history of narcotic addiction. The addiction was characterized by extreme psychic craving, euphoria, and tolerance to the drug. The patient stated that he took 36 tablets of the drug (1,152 mg) and over 7 gm of aspirin per day. He developed a classic case of acetylsalicylic acid intoxication. In the hospital, the patient was able to tolerate 780 mg of the drug. With doses of 600 mg orally, nonaddicted patients showed nausea, vomiting, sedation, and respiratory depression. Within 24 to 48 hours in the hospital, the patient showed definite withdrawal signs, including chills, profuse sweating, abdominal cramps, headache, nervousness, and diarrhea. This case suggests that a psychic addiction to dextro propoxyphene hydrocloride can occur.

Lafayette Clinic
Detroit, Michigan

682 Asatoor, A. M., Levi, A. J., & Milne, M. D. **Tranylcypromine and cheese.** (Letter) Lancet, 2(7310):733–734, 1963.

Toxic effects from ingestion of cheese in patients treated with potent monoamine oxidase inhibitors, such as tranylcypromine, are

eported. Tyramine is suggested as the toxic gent in cheese. Two normal, healthy adults onsumed a breakfast of 180 g Camembert and 25 g Stilton cheeses, respectively. In both xperiments, total phenolic acids, after acid ydrolysis of urine specimens, were estima- ed. Increase in extractable urinary pheno- ic acid was entirely due to a rise in p-hy- roxyphenylacetic acid, an acid derived from yramine by oxidation with monamine oxidase nd aldehyde oxidase. It was calculated that he excess of excreted p-hydroxyphenylacetic cid was derived from 70 mg of tyramine in he Stilton cheese and 230 mg of tyramine in he Camembert. Tyramine is a powerful pres- or agent. Normally, this amine is rapidly legraded to its nontoxic derivative, p-hy- roxphenylacetic acid, but in the presence of he enzyme inhibitor, it persists in body luids for a considerable time.

estminister Hospital
ondon, England

683 Dorrell, W., Mielczarek, J., Johnson, J., Miller, T. N. & Morgan, D. H. **ranylcypromine.** (Letter) Lancet, 1(7277): 88, 1963.

ive cases of side effects in patients being reated with tranylcypromine are reported. 47-year-old man treated with 10 mg tranyl- ypromine and 1 mg trifluoperazine t.i.d., nd a 59-year-old woman treated with 20 mg ranylcypromine t.i.d. and 10 mg chlordiaze- oxide t.i.d. developed intracranial bleed- ng, which imitated subarachnoid hemorrhage. n a girl of 19, an overdose of medication, consisting of 48 mg of tranylcypromine and 4 g of trifluoperazine, resulted in severe ypertension and headache. Treatment with 3 g pentolinium tartrate, a hypotensive drug, elieved the symptoms. A 24-year-old woman ecame addicted to tranylcypromine and tri- luoperazine. Consumption of medication eached 140 mg tranylcypromine and 14 mg tri- luoperazine a day. A 42-year-old man be- ame addicted to tranylcypromine and trifluo- erazine (120 mg and 12 mg per day, respec- ively). When this drug combination began to ose its effect, he began to take large doses f a sodium amylobarbitone and dexamphetamine ulphate combination in addition to the other edication. No ill effects developed from he large doses of the four drugs. Amphet- mine did not potentiate the antidepressant ffect of tranylcypromine.

No address)

684 Morton, Eric V. B. & Hall, J. E. **Side-effects of methaqualone.** (Let- ter) British Medical Journal, (5331):680, 1963.

A case of aplastic anemia following metha- qualone administration was previously re- ported. The correspondants, after 4 years of study of the animal and human pharmacol- ogy of methaqualone, found that the serious side effects listed in the original paper, including marrow depression, did not occur. In an attempt to learn more concerning the case where methaqualone was apparently the cause of marrow depression, it was discov- ered that methaqualone had been given in conjunction with a drug of unknown toxicity. They have not, as yet, received more factual data on the case, and until more is known, there is no evidence that methaqualone, given alone, causes serious side effects.

Boots Pure Drug Co., Ltd.
Nottingham, England

685 Montegriffo, V. M. **Hyperpyrexia dur- ing treatment with methyldopa.** British Medical Journal, (5348):35-36, 1963.

A hypersensitivity reaction, manifested by hyperpyrexia, in a 44-year-old woman being treated for hypertension by administering methyldopa, is reported. Methyldopa was given in 250-mg doses every 8 hours. On the ninth day of this medication, the patient became restless, disoriented in time, and agitated. The next day, her temperature was 106° F. All laboratory test were normal, but pyrexia persisted, fluctuating between 104° and 106° F. A generalized, nonirri- tant, erythematous rash developed. Methyl- dopa was discontinued, and within 12 hours, pyrexia subsided and the rash disappeared. When methyldopa was administered again, pyrexia and the rash returned. An attempt was made to show the presence of circulating antibodies using simple flocculation and gel-diffusion precipitation techniques, but no precipitins were found at any time.

(No address)

686 Johnson, Philip C., Jr., Charalampous, K. D., & Hug, A., eds. **University ward rounds. Psychosis following the use of am- phetamines.** Medical Record and Annals, 51(2):31-32, 1963.

Amphetamine psychosis often is indistinguish- able from paranoid schizophrenia, and fre- quent absence of disorientation may distract from the recognition of a toxic state. A high percentage of patients addicted to am- phetamines often use other agents concur- rently, such as alcohol, barbiturates, opi- ates, or bromides. Although many who devel- op amphetamine psychosis are of abnormal

personality, others are not. Because amphetamines are true hallucinogens and, a single dose of 50 mg can produce psychosis, the methyl orange test is recommended for differential diagnosis. False positive results due to other amines can be eliminated by using paper partition chromatography. The drug is excreted in the urine for as long as 7 days after withdrawal. Treatment is nonspecific, and abrupt withdrawal from the drug, hospitalization, and some sedation are advised.

Methodist Hospital
Houston, Texas

687 Womack, A. M. **Tranylcypromine.** (Letter) Lancet, (7305):463, 1963.

Case histories are given of three unusual reactions to tranylcypromine. In the first case, a youth died from taking tranylcypromine following ingestion of cheese. In the second case, a 38-year-old woman taking tranylcypromine died of petechial hemorrhage after a 12-hour illness. The only postmortem findings were petechial hemorrhages in the floor of the fourth ventricle, posterior limb of the lateral ventricle, and anterior surface of the heart. In previously reported cases of intracranial bleeding in patients treated with tranylcypromine, bleeding was massive and was associated with some other lesion or abnormality, such as congenital aneurysm. In this case, bleeding was not massive, nor was it associated with organic abnormality. Before onset of severe symptoms, the patient complained of headaches, and her blood pressure was high. In the third case, tranylcypromine was administered to a 36-year-old white woman suffering from porphysia. The drug produced dramatic improvement in her condition. The initial dose was 10 mg t.i.d., but this was reduced to 10 mg per day because of insomnia. Dosage was gradually reduced to 10 mg every third day and then to every fourth day. The patient was finally able to abandon the drug and continued to feel well.

(No address)

688 Berger, F. M. **Hazards of drugs in pregnancy.** (Letter) British Medical Journal, (5329):540, 1963.

A critical evaluation is given of a paper on the influence of meprobamate in pregnant rats. The paper reported that meprobamate administered to pregnant rats may have detrimentally altered the maze-learning ability of the offspring. The ability of rats to run the maze in 30 seconds or less in two out of three trials was taken as the criterion of learning. Rats used in these trials were smaller and less active than normal rats. Two comments are made on the conditions of these trials: (1) Rats showing motor impairment are not suitable for maze evaluation because performance will be indicative of impairment not of ability to learn. (2) Offspring of rats given similar or larger doses of meprobamate (dosage not given) throughout pregnancy grow normally, are not less active, and do not weigh less than offspring of untreated animals. Meprobamate is alleged to have an effect on brain development, yet no time-defined influence limited to critical stages of brain development was discovered under the conditions of the experiment.

Wallace Laboratories
Cranbury , New Jersey

689 Cohen, S. **The chemical extrapyramidal syndrome: Its reduction with UK-738.** Medicina Experimentalis, 8:101-106, 1963.

N-ethyl-nortropine-benzhydrylether-hydrobromide (UK-738) was tested for its effect in treating or in preventing the extrapyramidal syndrome (EPS), which is chemically produced by drugs with phenothiazine, iminodibenzyl, and reserpine structures. UK-738 is a condensation of the standard antihistaminics. Doses of UK-738 ranging from 4 to 32 mg per day (usually less than 10 mg per day) were administered to 171 chronic schizophrenics with moderate or severe manifestations of EPS while on phenothiazine. Of this group, 129 improved with UK-738, 27 improved with UK-738 and reduction of phenothiazine dosage, and 15 were unimproved. Eighteen patients who received 32 mg of UK-738 daily for 2 years developed no significant side effects; UK-738 in small doses (2 to 6 mg daily) successfully controlled the four primary manifestations of EPS (Dyskinesia, akinesia, akathisia, and parkinsonism) in most schizophrenic patients. UK-738 is produced as a syrup, which facilitates administration in patients with disorders of the swallowing mechanism.

Veterans Administration Center
Los Angeles, California

690 Thrower, James C. **Iatrogenic effect of drugs and anesthesia.** Journal of the South Carolina Medical Association, 59(1):1-6, 1963.

Care must be exercised in administering surgical anesthesia to patients who have been taking various psychoactive drugs. Diethyl ether and cyclopropane act as direct myocardial depressants, and halothane adds to the effect of antihypertensive agents. Any potentially offending or incompletely studied tranquilizer must be discontinued at least 72 hours preoperatively, including chlorpromazine, the phenothiazines, and the dicarbamates. The antihypertensives can cause profound cardiovascular collapse during anesthesia. Chlorthiazide should be discontinued 4 days before surgery, and Rauwolfia alkaloids or reserpine should be stopped 2 weeks before major elective surgery. Patients who have received cortisone during the previous 1 to 2 years may undergo minor or emergency surgery with preoperative and/or concomitant administration of cortisone. The oxytocics, such as pituitrin, may produce extensive coronary vasoconstriction under anesthesia. Trichloroethylene is to be discontinued several hours before administering anesthetic in the presence of soda-lime.

Charleston, South Carolina

691 Refshauge, W. D. **Phenmetrazine and trifluoperazine.** (Letter) Medical Journal of Australia, 1(3207):58, 1963.

Possible toxicity of phenmetrazine and trifluoperazine is discussed in association with the use of these drugs in pregnancy. Two children with extensive diaphragmatic hernias were born to a mother who took phenmetrazine in the 4th to 12th weeks of both pregnancies. Phocomelia, involving all four limbs, was reported in twins born to a mother who took trifluoperazine during the first 3 months of pregnancy. Eight other cases of congenital deformity were reported in which this drug had a possible association. Both drugs are restricted to prescription sale.

Director-General of Health
Canberra, Australia

692 Kane, Francis J., Jr. & Taylor, Terry W. **Mania associated with the use of I.N.H. and cocaine.** American Journal of Psychiatry, 119:1098-1099, 1963.

Mental disturbances accompanying the use of isonicotinic hydrazide and cocaine have been reported in the past. A case history is given of a man who developed similar attacks of mania, separated by a 30-year interval, associated on both occasions with the use of these drugs. The first attack of mania followed the use of cocaine extract intranasally for relief of sinusitis. The second attack followed the oral administration of 100 mg isonicotinic acid hydrazide (INH) q.i.d. The INH can cause CNS overstimulation by interfering with vital cerebral metabolic systems. Cocaine releases abnormal amounts of norepinephrine, which causes a central adrenergic stimulus similar to that provoked by LSD. Personal psychological stress plus impaired cerebral function seem to have been cofactors in the development of the patient's illness.

University of North Carolina
Chapel Hill, North Carolina

693 Moriarity, Andrew J. **Trifluoperazine and congenital malformations.** (Letter) Canadian Medical Journal, 88:97, 1963.

Doctor Andrew J. Moriarity reports on the possible teratogenicity of pharmaceutical products containing trifluoperazine. In Canada, eight cases with a possible association between congenital deformity and the use of trifluoperazine have been cited. Two women aborted between 3-$\frac{1}{2}$ and 4 months. Both had received cyclic hormonal therapy up to the time of conception, and another antiemetic was used as well. Two cases were discovered in a survey of possible "thalidomide cases." One woman with a history of a serious mental condition delivered at five months when being treated with stelazine in addition to other medications. The baby had osseous abnormalities in addition to multiple internal deformities. Thirty-six Canadian obstetricians reported on 409 patients. There were no reports associating trifluoperazine with congenital defects. On the basis of extensive chemical usage for over 4 years, as well as on a specific followup of approximately 700 cases where stelazine was used in studies of nausea and vomiting of pregnancy, a causal relationship has not been demonstrated between trifluoperazine therapy and congenital malformation of the types reported to be drug induced.

Smith Kline & French
Inter-American Corporation
Montreal 9, Quebec

694 Kane, Francis J., Jr. **Severe oral moniliasis complicating chlorpromazine therapy.** American Journal of Psychiatry, 119(9):890, 1963.

A case of severe oral moniliasis as a complication of chlorpromazine therapy is reported.

A 31-year-old man suffering from restlessness, agitation, excessive religiosity, and delusions concerning communication with God was treated with 800 mg of chlorpromazine daily in conjunction with 2 mg b.i.d. of benztropine methanesulfonate. Several days after treatment started, an examination revealed that the patient had a very reddened pharynx covered with small white spots and a tongue covered with a heavy brown and white coat. A dermatologist determined that the patient was suffering from a severe pharyngitis and glossitis due to candida albicans. Therapeutic response to 100,000 units q.i.d. of nystatin was good, and it was not necessary to discontinue chlorpromazine therapy. The severe dryness of mouth from which this patient suffered as a side effect of chlorpromazine medication may have sufficiently altered the normal flora and pH of the mouth to make a monilia infection more possible.

University of North Carolina
Chapel Hill, North Carolina

695 **Danger corner.** British Medical Journal, (5335):934, 1963.

The toxic effect of relatively nontoxic drugs when given in combination is discussed. Pethidine and the amine oxidase inhibitors, which are relatively nontoxic when given separately, can cause respiratory collapse and death when given in association. Certain antibiotics given to patients who are under anesthesia elicit the same toxic response. Neomycin and streptomycin in large i.p. doses can cause a neuromuscular blocking effect, which is additive to the effect of relaxant drugs used in anesthesia, such as succinylcholine chloride. Antibiotic dosage should be kept as low as possible, and its administration should be delayed for as long as possible after recovery of spontaneous respiration.

(No address)

696 Simpson, J. A., Evans, J. I., & Sanderson, I. D. **Amblyopia due to pheniprazine.** (Letter) British Medical Journal, (5326):331, 1963.

A 50-year-old patient suffering from an endogenous depressive illness, accompanied by severe headaches, was treated with 9 mg of pheniprazine daily for a period of approximately 30 months. After 15 months of therapy, the patient noticed deterioration of vision. Treatment was stopped after 30 months of therapy when the patient was diagnosed as having bilateral optic atrophy, complete color blindness, and a small cerebral visual defect. Since stopping pheniprazine, there has been no noticeable improvement, but no deterioration, in the patient's visions. Two conclusions can be drawn from this case report: (1) symptoms developing late, as well as early, in the course of drug therapy should be regarded with suspicion; and (2) where a toxic effect is suspected, the drug concerned should be withheld without delay.

Northern General Hospital
Edinburgh 5, England

697 Stratas, N. E., Phillips, R. D., Walker, P. A., & Sandifer, M. G. **A study of drug induced parkinsonism.** Diseases of the Nervous System, 24:180, 1963.

A study was conducted to determine the extent to which anti-Parkinson drugs are needed in patients receiving chlorpromazine and/or prochlorperazine therapy. A group of 88 hospitalized females, 25 to 55 years old receiving 80 to 3,100 mg (usually 200 to 300 mg) phenothiazine daily was evaluated for extrapyramidal signs. The anti-Parkinson drugs were then discontinued, and reevaluations were made over a period of 9 weeks. Of the 88 patients, 64 (73%) had no extrapyramidal signs and did not develop them when the anti-Parkinson drugs were withdrawn. Of the remaining 24 patients, 16 were placed on a reduced dosage of the same phenothiazines, and 8 were switched to thioridazine. Of the 16 placed on reduced dosage, 13 were free from extrapyramidal symptoms at the end of 2 weeks, and the other 3 responded to thioridazine. All 8 patients who were directly on thioridazine lost their extrapyramidal symptoms. Hyperactivity and agitation were noted in 4 of the 16 on reduced phenothiazines, but they regained their previous level of adjustment within 2 weeks.

(No address)

698 McKown, Charles H., Verhulst, Henry L., & Crotty, John J. **Overdosage effects and danger from tranquilizing drugs.** Journal of the American Medical Association, 185(6): 425-430, 1963.

Of 968 cases of tranquilizer ingestion reported to the National Clearinghouse for Poison Control Centers from July 1959

through December 1960, 378 (or 39.0%) involved ingestion of phenothiazine derivatives; 151 (15.6%) ingested Rauwolfia alkaloids; 280 (28.9%) ingested substituted diols; 115 (11.9%) ingested drugs of miscellaneous structure; 21 (2.2%) ingested combined drugs; and 23 (2.4%) involved multiple ingestion. Overdosage of tranquilizers resulted in moderate to severe central nervous system depression, occasional coma, a few cases of convulsions, and relatively rare extrapyramidal manifestations. The highest percentage of accidental ingestion was in the children, although fewer children required hospitalization than members of other age groups. The highest rate of suicidal attempts was found among the young adult and the adult groups. Although phenothiazines are being prescribed more frequently for relatively more severe mental disturbances, the figures indicate a greater proportion of suicidal attempts with minor tranquilizers.

National Clearinghouse
Poison Control Branch
U. S. Public Health Service
Washington, D. C.

699 Mann, Alan M. **Tranylcypromine cephalgia.** Canadian Medical Association Journal, 89:1115-1118, 1963.

Tranylcypromine, a useful antidepressant agent, has been linked with a clinical syndrome of undetermined incidence characterized by exceedingly severe and prolonged headache. Associated phenomena may include paroxysmal hypertension, pallor, chest pain, and collapse. This violent reaction does not seem to be related to age, sex, duration of treatment, or preexisting cardiovascular disease; nor is it possible to predict in whom it will occur. The clinical picture may sometimes be quite similar to that produced by subarachnoid hemorrhage or by pheochromocytoma. The mechanism of action is not known, although it is possible that the syndrome may be due to an amphetamine-like effect; i.e., that tranylcypromine influences the adrenergic component of the reticular activating system. The occurrence of severe headache in the course of tranylcypromine therapy is an indication for immediate withdrawal of the drug. Tranylcypromine cephalgia should be considered as part of the differential diagnosis of sudden, violent, and prostrating headache. (Author abstract)

Montreal, Canada

700 Low-Beer, G. A. & Tidmarsh, David. **Collapse after "parstelin".** (Letter) British Medical Journal, (5358):683-684, 1963.

A chronic schizophrenic who had been subject to asthmatic attacks from childhood, and who had developed edema of the tongue following a previous administration of prochlorperazine, was given chlorpromazine 100 mg t.i.d., iproniazid 50 mg t.i.d., and ephedrine 30 mg t.i.d. for 3 weeks, up until 4 days before his death, with no ill effect. Tranylcypromine plus trifluoperazine in a dosage of 1 t.i.d. was substituted for iproniazid, and ephedrine was prescribed to be given only during attacks of asthma. The day before his death, the patient felt vaguely unwell, and was given ephedrine 30 mg for the first time since tranylcypromine plus trifluoperazine was started. Four hours later, his temperature rose to 100° F and was accompanied by shivering and sweating. One and one-half hours later, he suddenly became cyanosed, sweated profusely, stopped shivering, and his pulse was almost impalpable. In spite of an i.v. of 100 mg promazine, 0.5 g aminophylline, 0.5 g nikethamide, and oxygen inhalation, he died shortly thereafter. Autopsy showed a liver temperature of 100° F and signs of a mild asthmatic attack, but there were no other abnormal findings. The cause of death was attributed to hyperpyrexia due to idiosyncrasy to tranylcypromine--trifluoperazine.

Epsom, Surrey
England

701 Blackwell, B. **Hypertensive crisis due to monoamine-oxidase inhibitors.** (Lancet, 2(7313):849-851, 1963.

Twelve patients, 2 male and 10 female all under 50 years of age, who had hypertensive crises from treatment with monoamine oxidase inhibitors were studied. Eleven patients were receiving tranylcypromine, and in 8 of these, the drug was combined with 1 mg of trifluoperazine; 1 patient was taking amphetamines concurrently; and 1 patient was receiving phenelzine. There was no constant time relation between taking the tablets and onset of symptoms. None of the patients were taking an excessive dose, and there was wide variation in duration of medication (from 3 days to 16 months). Three patients were able to continue taking the drug without recurrence of symptoms. These features of the crises do not suggest a normal toxic response or an idiosyncratic response; rather, the possibility of an exogenous precipitating factor is suggested. This supposition is supported by an examination of the dietary history of the patients. There is evidence

that the crises are precipitated by amphetamine and cheese protein. The symptoms, physiological changes, and mode of fatal termination of the hypertensive crises are thought to resemble those of pheochromocytoma.

Charing Cross Hospital
London, England

702 Bradley, J. J. & Francis, J. G. **Side-effects of monoamine oxidase inhibitors.** (Letter) British Medical Journal, (5329):539, 1963.

A study is conducted on the incidence and mechanism of undesirable reactions when patients, who are being treated with monoamine oxidase inhibitors, receive pethidine or opium derivatives. Of the 12 cases reported, 3 were observed under the present study. It is important to discover: (1) whether this side effect is a common and invariably alarming complication; or (2) whether it depends upon a rare idiosyncrasy.

St. Thomas's Hospital
London, England

703 Miller, Morton. **Neuropathy, agranulocytosis, and hepato-toxicity following imipramine therapy.** American Journal of Psychiatry, 120:185-186, 1963.

A 66-year-old white female, being treated for agitated depression, developed bilateral peroneal palsy, agranulocytosis, and hepatotoxicity following therapeutic administration of imipramine. Dosage was 150 mg per day of imipramine combined with 40 mg per day of chlordiazepoxide. Laboratory tests ruled out other possible sources of symptoms noted. Five previously reported cases of motor neuropathy appearing during imipramine therapy are similar, in that all involved elderly persons, and were restricted to the lower extremities. Involvement of the sensory nervous system is less frequently observed. Neuropathic symptoms do not always cease when imipramine administration is discontinued. The large variety of neurotoxic side effects from imipramine suggest that caution be exercised in the use of this agent in pregnancy.

Yale University School of Medicine
New Haven, Connecticut

704 Erslev, Allan J. **Drug-induced bone marrow suppression.** Pennsylvania Medical Journal, 66:31-34, 1963.

The development of chloramphenicol as a therapeutic agent is discussed in terms of its tendency to induce bone-marrow suppression. Greater cooperation from drug companies and physicians, and the use of safeguards (white cell counts, hemoglobin concentration, reticulocyte counts) once treatment is begun, should reduce the incidence of fatal, drug-induced aplastic anemia.

Jefferson Medical College
Philadelphia, Pennsylvania

705 Palmer, C. A. L. **Toxic amblyopia due to pheniprazine.** (Letter) British Medical Journal, (5322):38, 1963.

Deterioration of visual acuity and red--green color blindness appeared in two men, 41 and 53 years of age, and two women, 53 and 66 years of age, who had been taking 6 to 12 mg pheniprazine daily for 4 months to 1 year. Cessation of treatment was followed by gradual or rapid improvement in visual acuity and by at least partial improvement of amblyopia or trichromatism. Pheniprazine, the most potent of the MAO inhibitors, is no longer marketed in England, following reports of fatal liver damage and of visual disturbances. Tobacco was eliminated as an etiological factor in the above four cases.

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Manchester Royal Eye Hospital
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See also: 590, 596, 599, 600, 607, 622, 623, 631, 641, 643, 644, 648, 650, 652, 654, 656, 657, 659, 660, 666, 667, 669, 672, 674, 723, 726, 729, 732, 733, 735, 736, 739, 758, 786

706 Whitman, Roy M. **Drugs, dreams and the experimental subject.** Canadian Psychiatric Association Journal, 8(6):395-399, 1963.

Four major studies utilizing rapid eye-movements (REM) indicators of dreaming are being conducted at the university psychiatry department. Primary findings in the first study, the psychological effects of tranquillizers, concerned the effects of imipramine, which diminished the number of dreams per night and increased the amount of hostility expressed in these dreams. Anxiety and dependency also increased. The expression of heterosexuality was increased by prochlorperazine and that of homosexuality was increased by phenobarbital. In the second study, volunteers' concerns about the experiment fell into four categories: anxiety about the experimenter, the experimental room, the experimental equipment, and their own behavior. The third study, of experimentally produced conflicts, indicated that the conflict experienced by the subject was not an exact replica of the one suggested by a hypnotist. It is, rather, an amalgamation of that conflict with his relationship to the hypnotist, his previous personality, and his relationship with the two interviewers. The last study was a comparison of the dreams as reported to the therapist and to the experimenter. It was found that the material is altered or drops out according to the nature of the subject's relationship with the experimenter and the therapist.

University of Cincinnati College of Medicine
Cincinnati, Ohio

707 Forney, Robert B. & Hughes, Francis W. **Behavioral effects on the rat of benzquinamide and benzquinamide-alcohol combinations.** Archives Internationales de Pharmacodynamie et de Therapie, 142(1-2):237-242, 1963.

Tranquilization in rats was evaluated quantitatively by first training them to avoid a shocking stimulus. Then, the test drugs were administered, and anxiety production and performance were compared——an ideal tranquilizer would reduce anxiety but would not diminish performance. Benzquinamide was used in dosages of 10, 20, and 30 mg per kg i.p. alone or in combination with 0.5 g per kg of ethanol. Ten rats were used for each dosage of the drug and for each combination of the drug and alcohol. The test period consisted of three trials per rat every 15 minutes for 4 hours. Benzquinamide effectively reduced anxiety without appreciably altering performance in doses of 10 and 20 mg per kg. At 30 mg per kg, there was also a great reduction in performance and an increase in the number of trials in which the animals did not respond to light or shock. When alcohol was given along with 10 mg per kg of benzquinamide, a greater tranquilizer index was effected because the period of activity was extended. As the dose of the drug was increased and combined with alcohol, viz., at 20 mg per kg, there was no tranquilizing effect, and at 30 mg per kg, there was a profound inability to respond to stimuli. Benzquinamide is considered an effective tranquilizer of relatively short duration of action and effecting a minimal depreciation of performance. Alcohol profoundly increased the depressant character of the drug and diminished the ataractic property. This effect persisted after the alcohol had disappeared from the blood.

Indiana University School of Medicine
Indianapolis, Indiana

708 Ehrentheil, Otto F. **Thought content of mute chronic schizophrenic patients: Interviews after injection of amobarbital sodium (sodium amytal) and methamphetamine hydrochloride (methedrine).** Journal of Nervous and Mental Disease, 137(2):187-191, 1963.

This exploratory study was undertaken to discover the main thought content and interest of schizophrenic men who had not spoken for many years and were withdrawn. Three men (46, 65, and 66 years old) who had talked best in a previous experiment were selected. Injections (i.v.) of 0.5 g of sodium amytal in solution were followed by 20 mg of methamphetamine HCl (to overcome sleepiness), and the patients were temporarily relieved of muteness. Detailed case histories and transcripts of the interviews of the three patients are given along with those of a fourth

schizophrenic who was mute but not withdrawn. The results of this experiment show that the apparent similarity of these patients disappeared as soon as they spoke. The different educational levels and backgrounds, the different aims in life, and the different frustrations became evident. Withdrawn, mute patients are thinking about events that occurred before or at the time of their psychotic break. Although muteness is often a manifestation of withdrawal, it does not always signify withdrawal. This was illustrated by the report about a mute, but not withdrawn, patient who later improved and talked, revealing that he had observed the events around him during the time of his muteness.

54 Wallingford Road
Brighton, Massachusetts

709 Geller, I., Bachman, E., & Seifter, J. **Effects of reserpine and morphine on behavior suppressed by punishment.** Life Sciences, 4:226-231, 1963.

Suppression of behavior was conditioned in 12 hungry rats by simultaneously rewarding with food and punishing with electric shocks all lever responses made in the presence of a tone stimulus. Six rats received reserpine (0.23 mg per kg i.p.) for 18 days; drug injections followed each experimental session. In predrug control sessions, hungry rats would tolerate only 1 to 4 shocks in order to obtain food. Under reserpine, the rats showed an increase in number of shocks tolerated. All of the reserpinized rats showed a gradual decrease in variable-interval response rate as the drug doses continued. In 6 other rats receiving chronic administrations of morphine sulphate at gradually increasing doses (1.0 to 4.0 mg per kg), results were ineffective.

Wyeth Laboratories, Inc.
Philadelphia 1, Pennsylvania

710 Haertzen, Charles A. & Hill, Harris E. **Assessing subjective effects of drugs: An index of carelessness and confusion for use with the Addiction Research Center Inventory (ARCI).** Journal of Clinical Psychology, 19(4):407-412, 1963.

To develop an index of consistency for estimating reliability of response, a group of 219 male, former narcotic addicts who were predominantly social deviants or psychopaths (with some degree of neurotic or schizoid tendency) was studied. The Ca scale of the Addiction Research Center Inventory, comprised of items that are repeated identically or in opposite form, was used as a measure of validity. Comparison of Ca scores obtained under varying conditions (no-drug, placebo, chlorpromazine, LSD-25, morphine, pentobarbital, amphetamine, pyrahexyl, and alcohol) shows that the scale is insensitive to some forms of drug-induced inconsistency. Comparison of these scores with the MMPI-F scale for malingering, the Shipley vocabulary test of illiteracy, and with overt signs of carelessness also indicates that the Ca scale measures certain aspects of carelessness and illiteracy. Results indicate that a considerable degree of the "systematic inconsistency," found under some conditions, is due to drug-induced alteration in response hierarchies.

National Institute of Mental Health
Addiction Research Center
Lexington, Kentucky

711 Alnaes, Randolf & Aslanov, Anatoli. **Die Wirkung von Imipramin auf die höhere Nerventätigkeit des Menschen. Eine experimentelle Untersuchung mit der Methodik der bedingten Reflexe. (Effect of imipramine on the higher nervous activity of man. An experimental investigation using the conditioned reflex method.** Archiv für Psychiatrie und Nervenkrankheiten vereinigt mit Zeitschrift fur die Gesamte Neurologie und Psychiatrie, 204:133-141, 1963.

The effect of a single dose of imipramine (25 mg tablet) was observed on the psychological and physiological processes of 14 healthy volunteer subjects, 8 female and 6 male. No placebo control was used. The speed and quality of response in word-association tests were measured. Pulse, blood pressure, and threshold of the defense reaction to an electric impulse were used as criteria of lower nervous activity. Cortical functions of concentration, attention, accuracy, and perseverence were measured by a proofreading test. Results showed an increase in reaction time, indicating inhibition of the complex structures of the cortex. Onset of a tired feeling and depression in mood, 2 hours after taking the imipramine, indicate inhibition of the subcortical structures. The tired feeling decreased somewhat in the following 2 or 3 hours, and the mood of the subject improved, indicating disinhibition of the subcortical structures (positive induction). This may result from removal of active inhibition, in which ability to differentiate is lost, but a facilitating subcortical effect is possible (negative induction). The test with electric current showed a higher threshold of defense reaction, or inhibition of unconditioned motor reactions, contradicting clinical experience to the effect that imipramine has better effect on endogenous than on reactive depressions.

ustad-Hospital
lo, Norway

2 Swinyard, Ewart A., Miyahara, James T., Clark, Lincoln D.,& Goodman, Louis **The effect of experimentally-induced ress on pentylenetetrazol seizure thresh-d in mice.** Psychopharmacologia, 4:343-3, 1963.

idence is presented that a disturbed emo-onal state experimentally induced in mice a stressful environment lowers the thresh-d for pentylenetetrazol seizures. Novice ult male albino mice were used as experi-ntal animals. The convulsant solution, mposed of 0.5% pentylenetetrazol, 0.9% dium chloride, and 10μg per ml of heparin dium was infused into the tail vein at a nstant rate of 0.005 ml per second until e mouse exhibited persistent clonus for 3 conds. Body weight and infusion time to d point were recorded for each experimen-l and control animal. The effect of 20 nutes of intermittent foot shock on spon-neous activity and on overt behavior was corded. In addition, the effect of pain-duced conditioned emotional response and total-body immobilization and postural sequilibrium on the seizure threshold was termined. Foot shock decreased spontane-s motor activity and induced immobility, ouching, and increased defecation. The her stress situations lowered seizure reshold. Data are given indicating a di-ct relation between the reduction in sei-re threshold and the intensity of dis-rbed state. The observed increase in ain excitability caused by apprehension d anxiety may result from the effect of dogenously released catecholamines on the ntral nervous system.

iversity of Utah
llege of Pharmacy and College of Medicine
lt Lake City, Utah

3 Mercier, Jacques & Dessaigne, Suzanne. **Influence exercée par les hypnotiques, anquillisants et neuroplégiques sur le mportement agressif de la Mante religieuse. nfluence exerted by hypnotics, tranquili-rs and neuroplegics on the aggressive be-vior of the praying Mantis.)** Comptes ndus des Seances de la Societe de Biologie des Ses Filiales, 156:110-114, 1962.

fteen female praying mantises were inject-in the dorsal vessel, and reactions stud-d to being picked up with tweezers, as ll as to control subjects of the same spe-es. The insects were observed in a glass bowl 30 cm in diameter, containing fine soil, and illuminated by a 40-watt electric bulb. A weak dose (50μg per g) of mebubarbital produces motor difficulties and suppresses the hunting instinct, but not defense reactions. Large dosage (100μg per g) produces reversible narcosis. Procalmadiol reduces, but does not suppress, aggressiveness and voracity at doses evoking pronounced motor difficulty and loss of balance. At larger dosage (500μg per g), aggressiveness disappears for 24 hours. Chlorpromazine (5μg per g) briefly suppresses aggressiveness and defense reactions without affecting motor activity. Strong (50μg per g) dosage disturbs motor activity and produces a state of indifference. Aggressiveness reappears in 18 hours, but voracity is suppressed. Reserpine has delayed action somewhat similar to its effect in mammals. A small dose (20μg per g) produces a fixed attitude resembling catatony in higher animals. It decreases or suppresses aggressiveness, but does not appear to alter vigilance or defense reaction. The effects lasted 24 hours. The above effects in this insect suggest the possibility of peripheral effects in mammals.

College of Medicine and Pharmacy
Marseille, France

714 Frankenhaeuser, Marianne. **Effects of nitrous oxide on subjective and objective variables.** Scandinavian Journal of Psychology, 4:37-43, 1963.

Effects of nitrous oxide in different subanesthetic concentrations were studied in twelve subjects. Subjective scales of intoxication and of eight other mood variables were obtained by the method of magnitude estimation. Objective performance was examined by memory and arithmetic tests. For most variables, the dose-response curves obtained showed progressively larger effects with increasing dose levels. At concentrations below 20 percent, the changes were, on the whole, very slight. The results are compared with similar data from an experiment with alcohol. (Author abstract, edited)

University of Stockholm
Stockholm, Sweeden

715 Pishkin, Vladimir, Wolfgang, Aaron, & Bradshaw, F. J., Jr. **Hydroxyzine in concept identification under induced stress with chronic schizophrenics.** Journal of Nervous and Mental Diseases, 137(4):322-328, 1963.

To assess the psychotropic effects of hydroxyzine upon concept identification and

induced stress of schizophrenic subjects, a double-blind study was conducted with 72 males with chronic undifferentiated schizophrenia. The subjects were 25 to 50 years old, with mean age of 37.82 years; mean length of hospitalization was 9.36 years, with a range of 3 to 11 years. All continued taking varying amounts of chlorpromazine (to 150 mg maximum) during the study. The subjects were randomly assigned to 12 experimental conditions, as follows: 3 problem types (form, size, or number as relevant dimension); 3 degrees of complexity (1, 3, or 5 irrelevant information dimensions); and 2 drug conditions (hydroxyzine or placebo). The concept-identification task consisted of responding to a series of geometric patterns by pressing one of two keys. The subjects were given 1 mg per lg i.m. hydroxyzine or placebo, 30 minutes before the experiment. Each subject was conditioned to a 500 cycle per second tone of 2 seconds duration, followed by an electric shock for 2 seconds at intervals of 1 minute for 10 trials. Results showed no significant difference in the number of trials completed by the two groups within the 20-minute period. The drug effect did not reach significance in the test of speed of extinguishing the anticipatory galvanic skin response, nor in less interference with concept--identification performance. Changes in conductance were significantly greater with placebo than with hydroxyzine.

Veterans Administration Hospital
Oklahoma City, Oklahoma

716 Eisenberg, Leon, Lachman, Roy, Molling, Peter A., Lockner, Arthur, Mizelle, James D., & Conners, C. Keith. **A psychopharmacologic experiment in a training school for delinquent boys: Methods, problems, findings.** American Journal of Orthopsychiatry, 33:431-447, 1963.

A 10-week double-blind study was made of committed delinquent boys 11 to 17 years old, with an average age of 13 to 14 years. They received either an elixir of 5 to 40 mg per day dextroamphetamine, or a placebo of muscatel wine and sucrose, or no drug. At maximum dosage, the subjects received 3 cc of alcohol, which was divided into two doses daily. Symptom scoring was based on behavior ratings by cottage parents and class teachers, recorded at 3- or 4-week intervals, with three ratings before treatment, three during treatment, and one 3 weeks after treatment. The three subject groups did not differ significantly on either cottage or school ratings before treatment. At the conclusion of treatment, the drug group was significantly superior to both the placebo and control groups; the latter two groups did not differ significantly from each other. There were no longer any significant differences among the groups 3 weeks after treatment. The Bowers and Larson Class Play classification showed that the drug subjects were assigned fewer negative roles by peers, although there was no significant difference among the 3 groups in self-perception. The one toxic reaction of significance was a loss of weight in drug-treated subjects when a dosage of 30 mg per day was administered.

Johns Hopkins University School of Medicine
Baltimore, Maryland

717 Hankoff, Leon D., Engelhardt, David M., Freedman, Norbert, Mann, David, & Margolis, Reuben. **Denial of illness in relation to differential drug response.** Journal of Nervous and Mental Disease, 137:29-41, 1963.

The relation of attitude toward illness and response to psychopharmacologic treatment was studied in 170 chronic schizophrenic outpatients. The patient's attitude toward his illness was rated by the interviewing psychiatrist at the initiation of treatment in terms of the patient's acceptance or denial of signs and symptoms of mental illness. Patients were divided into three categories---acceptance, intermediate (admit mental illness in past or when questioned about it), and denial. Medication was prescribed according to a prearranged, randomized list. Three agents, promazine, chlorpromazine, and placebo, were used in identical capsule form. Dosage varied at the physician's discretion. After three months' treatment, measures of outcome included the psychiatrist's judgment of overall change in the patient and three quantitative measures---anxiety level, thought disorder, and social pathology. With placebo usage, a gradient of improvement rates for thought disorder by attitude group was seen: denial group 12.5 percent; intermediate group, 20.6 percent; and acceptance group, 53.9 percent. Using the placebo results as a model for comparison, a significant drug effect was seen for the intermediate group, with chlorpromazine showing an improvement rate of 63.2 percent. For the acceptance group, all agents were closely matched; about half of these patients showed improvement. For the denial group, promazine had the highest improvement rate, 46.7 percent. Findings are interpreted in the context of a disturbance of communication between patient and doctor; the influence of treatment orientation lies in its effect on communication.

State University of New York
Downstate Medical Center
Brooklyn, New York

8 Meier, Gilbert W., Hatfield, Jimmy L., & Foshee, Donald P. Genetic and behavioral aspects of pharmacologically induced arousal. Psychopharmacologia, 4:81-90, 63.

previously reported studies, clear differences have been shown among strains of bred mice in response to a variety of novel tuations and to certain pharmacologic ents. The present study tests the hypothis that such behavioral differences be- een genetically distinct groups may be a nction of arousal system differences. fty male mice, 60 to 65 days old, of each four inbred strains were selected that ow related differences in normal activity: LB/c, C3H/An, DBA/2, and C57BL/6. These ce were distributed randomly among four ug experimental groups and one control oup. Four drugs were chosen that could oduce measurable changes on an arousal ntinuum from sleep (pentobarbital 60 mg r kg), through quiescence (chlorpromazine mg per kg) and alertness (dextroampheta- ne 25 mg per kg), to convulsions (penty- enetetrazol 60 mg per kg). The control oup received isotonic saline as the pla- bo. Injections were made i.p. in dosages ccording to weight. Only the responses to entobarbital and dextroamphetamine were ntirely consistent with an arousal hypothsis, but significant strain differences apeared in base-activity levels, as well as n the responses to the standard doses of the rugs and of the placebo. The duration of he effect of pentylenetetrazol was also conistent, but the latency of that effect was ot. At best, the effect of chlorpromazine as that of a mild stimulant.

aboratory of Perinatal Physiology
uerta de Tierra Station
an Juan, Puerto Rico, USA

19 Rushton, Ruth & Steinberg, Hannah. **Dose-response relations of amphetmine-barbiturate mixtures.** Nature, 97(4871):1017-1018, 1963.

wo series of experiments were run with ister hooded female rats, aged 115 to 140 days, to determine dose-response relations f amphetamine—barbiturate mixtures and amhetamine and barbiturate administered seprately. In the first series, amphetamine sulphate and amylobarbitone sodium were studied separately and in combination (in a 1:20 ratio). In the second series, deamphetamine sulfate and amylobarbitone sodium were given in a ratio of 1:6.5. To study the relation of spontaneous activity and ataxia, records of the rats' footprints were obtained during a standard run, and their spacing was analyzed. To measure spontaneous activity, rats were placed in Y-shaped runway; the number of times an animal entered the arms with all four feet was the measure of activity. In the first series, doses of amphetamine ranged from 0.19 to 12.0 mg per kg; barbiturate ranged from 3.75 to 240 mg per kg. In the second series, dexamphetamine ranged from 0.30 to 9.44 mg per kg; barbiturate ranged from 1.88 to 60.0 mg per kg. For both experiments, the peak activity with the drug mixtures was greater than activity with any of the doses of the separate drugs. Peak activity occurred at the 0.75 amphetamine—15.0 amylobarbitone dose level in the first series and at the 1.18 dexamphetamine—7.5 amylobarbitone dose level in the second series. In the first series, ataxia first appeared at the peak-activity dose of the mixture; in the second, ataxia first appeared at double the peak-activity dose. The highest doses of all three drugs almost completely inhibited activity.

University College
London, England

720 Dorsch, W. & Hebenstreit, B. v. **Die Wirkung eines Fluphenazin-Dihydrochlorids auf die Fahrtauglichkeit. (Effect of fluphenazine dihydrochloride on driving ability.)** Arzneimittel-Forschung, 12:1074-1079, 1962.

To determine the effect of normal therapeutic doses of fluphenazine dihydrochloride on concentration, perception, and physical fatigue, a double-blind study of 24 students was conducted over a period of 8 weeks. The medication contained 20 mg phenylethylbarbituric acid per dose. Normal therapeutic dosage of a 1 mg tablet daily was administered for 1-week periods, and a placebo was given on alternate weeks. The study consisted of two parts: a cross-section study, investigating general psychophysical driving performance under the effects of medication and of placebo; and a longitudinal-section study of the change in driving performance under the influence of medication or placebo. Six persons were used in a modified test in which 3 were given the drug, and 3 were given the placebo for 14 days before switching. The tests used were hand and foot movements in response to various colored lights, measuring reaction time to optic or acoustic signals, selection of words from printed text, arranging numbered cards, adding columns of numbers, and pen pressure in writing. The results of both parts of the test showed no physiological or pathological deviation from the norm. The subjects reported no side effects. (Continued on next page)

Physiological-Medical Research Facility
Technical Control Society of Bayern
Munich, Germany

721 Benešová, O. **The effect of d- and l-phenmetrazine on the self-stimulation in rats.** Activitas Nervosa Superior, 5:1-3, 1963.

The effect of d- and l-phenmetrazine on self-stimulation was studied in a group of 17 Wistar rats of both sexes, weighing 220 to 280 g. Bipolar electrodes of constantan wire 0.17 mm in diameter were implanted into the posterior hypothalamus of the rats. By pressing a lever, the rats could give themselves electrical stimulation. The stimulation acts as either reward or punishment, which can be objectively and quantitatively measured by recording the frequency with which the rat presses the lever. The rate of self-stimulation was recorded for a 30-minute interval 2 days before the test, on the day of the test, 10 minutes following administration of phenmetrazine, and on the day after the test. Both d- and l-phenmetrazine were administered in a dose of 5 mg per kg i.p. Experiments were made in cross tests at weekly intervals. The l-isomer increased self-stimulation by 209%; the d-isomer increased self-stimulation by 33¼%.

Medical Faculty of Hygiene
Prague, Czechoslovakia

See also: 646, 655, 758, 768

PHARMACOLOGY

22 Bickel, M. H., Sulser, F., & Brodie, B. B. **Conversion of tranquilizers to ntidepressants by removal of one n-methyl roup.** Life Sciences, 4(4):247-253, 1963.

nvestigation was carried out with three hemically related structures: iminodiben- yls, dibenzocycloheptadienes, and phenothi- zines. Prototypes of these groups are des- ethylimipramine, desmethylamitriptyline, nd desmethylpromazine. In the antidepres- ant test, Sprague--Dawley rats (180 to 200) were given 10 to 40 mg per kg antidepres- ant i.p., followed 30 minutes later by 15 g per kg i.p. of RO 4-1284. The RO 4-1284 vokes a full reserpine response. Pretreat- ent with desmethylimipramine completely locks the reserpine syndrome, and many of ts signs are reversed to the opposite ex- remes of physiological and behavioral per- ormance. Some iminodibenzyls (mono- and i-demethylated analogues of imipramine) locked both the reserpine syndrome as well s the hyperactivity typical of desmethyl- mipramine. Most phenothiazines tested, in- luding chlorpromazine, promazine, and tri- flupromazine, did not block the reserpine yndrome. However, desmethylpromazine showed eak action, and desmethyltriflupromazine howed strong antireserpine action. When esmethylimipramine and RO 4-1284 are given to large groups of rats, only 70% of the nimals display full hyperactivity. The re- erpine syndrome is blocked, but not re- versed, in the remaining 30%. The propor- tion of animals that became hyperactive in- creased with increase in desmethyltrifluprom- azine dosage, but this proportion seemed to approach a limiting value of about 50%.

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723 Steiner, Wm. G., Pscheidt, G. R., Costa, E., & Himwich, H. E. **α-ethyltryptamine (etryptamine): An electroencephalographic, behavioral and neurochemical analysis.** Psychopharmacologia, 4:354-366, 1963.

In New Zealand male albino rabbits, etryptamine produced immediate EEG arousal with intracarotid and delayed EEG arousal with i.v. injection at all dosages of all isomers. Atropine sulfate and chlorpromazine reversed the arousal pattern. Methyl lysergic acid butanolamide pretreatment enhanced arousal, and tranylcypromine pretreatment produced alternation between arousal and sleep-like activity. None of the etryptamine acute doses of 5 to 80 mg per kg, i.p., increased the norepinephrine level in the brain of adult female Wistar rats within 1 to 24 hours. Rats receiving 8 mg per kg, i.p., twice a day showed a 68% increase on the 7th day. Little or no change in behavior was noted in the rats given 5 mg per kg etryptamine. At a dosage of 20 to 30 mg per kg, rats exhibited pronounced behavioral effects in a 3- to 4-hour period. The rats were hypersensitive to auditory stimuli, had tense musculature, motor weakness, and incoordination. All rats receiving etryptamine in combination with 1 mg per kg atropine sulfate or 2 mg per kg tranylcypromine became hypersensitive and displayed the same behavioral signs as those with etryptamine alone. Rats treated with 6 mg per kg pheniprazine, however, were indistinguishable from control animals in motor activity and behavior. Etryptamine was toxic at 68 to 80 mg per kg over a 10- to 24-hour period.

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724 Murphree, Henry B. **Effects in human volunteers of subparalytic doses of dihydro-β-erythroidine.** Clinical Pharmacology and Therapeutics, 4:304-410, 1963.

Dihydro-β-erythroidine, a curariform alkaloid isolated from the plant genus Erythrina americana, was tested in subparalytic doses in 18 trained human volunteers, none of whom had gross psychiatric illness. Unlike curare, this alkaloid is a tertairy amine; it can be given orally and can cross the blood--brain barrier. After experimentation with several dosage levels, two doses, 200 mg and 6 mg per kg, were selected to determine differential effects at different dosage levels. Single oral doses of 200 mg were given to 12 of the 18 volunteers; several weeks later, 6 mg per kg doses were given to 14 of the 18. At 200 mg, effects were bradycardia and visual difficulty, most

often described as blurring of vision or a double vision. The 6 mg per kg dose produced bradycardia and visual difficulty, plus hypotension and reduction in grip strength, with accompanying feelings of sedation. The onset of action of the drug at both dose levels was rapid, occurring 15 to 30 minutes after dosage. Visual effects and reduction in grip strength were highly correlated. Dihydro-β-erythroidine is readily absorbed when given orally, but its effect on skeletal muscle is erratic and not clearly related to body build. The central effect of the drug is one of mild intoxication or sedation which is less prominant than other effects. No stimulant or psychotomimetic effects occurred.

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725 Eckhardt, Eileen T. & Plaa, Gabriel L. **Role of biotransformation, biliary excretion and circulatory changes in chlorpromazine-induced sulfobromophthalein retention.** Journal of Pharmacology and Experimental Therapeutics, 139:383-389, 1963.

Male Swiss albino mice, weighing 18 to 30 g, and male Holtzman rats, weighing 350 to 400 g, were used in all experiments. Data are reported on: (1) the effect of chlorpromazine (6.3 mg per kg, p.o.) on the plasma ratio of free sulfobromophthalein sodium (BSP) and its major metabolite (MBSP) 30 minutes after administration of the dye (150 mg per kg, i.v.); (2) the effect of chlorpromazine (30 mg per kg i.v.) on BSP (50 mg per kg, i.v.) excretion in rats with acute bile fistulas; (3) the effect of varying doses of chlorpromazine on clearance of BSP (10 mg) in isolated, perfused rat livers; (4) comparative effects of chlorpromazine (6.3 mg per kg, p.o.) and carbon tetrachloride (1 ml per kg, p.o.) on 30-minutes BSP retention in mice 2 and 24 hours after pretreatment; and (5) the effect of i.v. ephedrine (20 mg per kg), atropine (2 mg per kg), diphenhydramine (10 mg per kg), phentolamine (5 mg per kg), barbital (275 mg per kg), and chlorpromazine (15 mg per kg) on the BSP plasma dye-disappearance curve in mice. The data indicate that phenothiazine-induced plasma retention of BSP in vivo is not due primarily to impaired metabolism or excretion, but to a decrease in hepatic blood flow. Vasoactive agents can affect the rate of BSP uptake from plasma, and carbon-particle distribution in the liver is altered by chlorpromazine treatment in a manner that is consistent with the concept of hepatic schemia.

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726 Magee, W. L. & Rossiter, R. J. **Incorporation of inorganic P^{32} into phospholipids of brain slices. Effect of certain tranquillizing drugs.** Canadian Journal of Biochemistry and Physiology, 41:1155-1162, 1963.

Fresh brain tissue (98 to 102 mg) from adult guinea pigs was added to Warburg flasks containing a measured quantity of Krebs-Ringer medium, buffered at pH 7.4, and glucose (11 millimoles). The vessels were gassed for 10 minutes with 100% oxygen, and the P^{32} was added. After equilibration at 37.5° C, the oxygen consumption was measured during a 2-hour incubation period. The phenothiazine derivatives, promazine, tetrameprozine, chlorpromazine, and 10-(3-dimethylaminopropyl)-2-acetophenothiazine maleate (WY 1172), increased the phospholipid labelling of brain slices when added in concentration of 0.1 millimole. Stimulation was most pronounced with chlorpromazine. At a concentration of 1.0 millimole, all the phenothiazine derivatives inhibited the labelling of phospholipid. Promethazine also acted like the above four drugs. At a concentration of 1.0 millimole, labelling was greatly inhibited, although at concentrations below 1.0, no increase in oxygen consumption, production of lactic acid, or concentration of phosphocreatine was observed. Over a wide range of concentration, methylene blue, a phenothiazine derivative, did not stimulate incorporation. Pipradrol, mepazine, and benzhydrol also stimulated P^{32} incorporation, but meprobamate did not; phenoglycodol caused only slight stimulation.

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727 Adjarian, Rose L. **Phenothiazine derivatives and local inflammation.** Archives Internationales de Pharmacodynamie et de Therapie, 141(3-4):443-456, 1963.

The local irritation from parenteral administration of phenothiazine drugs was studied using 6.484 R.P. [3-ethyl-10-(3'-dimethylamino-2'-methylpropyl)phenothiazine HCl]. The possibility of a relationship between fibrin clot, irritation, and rate of adsorption was investigated. In vitro trials, increasing volumes (0.1 to 0.8 cc) of 5%, 0.5%, 0.05%, and 0.005% 6.484 R.P. were added to a series of test tubes containing 1 cc bovine plasma. Fibrin clot occurred at all concentrations except 0.005%. In identical tests with defibrinated plasma, no gel formation occurred. Two in vivo trials were made. In the qualitative evaluation, New Zealand white female rabbits, 2.5 kg, and Wistar albino female rats, 150 g, were given 2.5% and 5%

lutions (in physiological saline) of 6.484 P., s.c., into dorsal air sacs in doses of mg per kg, rabbits, and 60 mg per kg, ts. In the quantitative evaluation, Wistar bino female rats, 150 g, were given s.c. in e left hind foot 0.03 cc of 6.484 R.P. lutions in varying concentrations in physiological saline or in buffers of varying onic strength. In the qualitative tests, a elatinous mass formed in both species in the nterior wall of the pouch within 24 hours, ut it was gone after 1 week. Central necrois of the dorsal sac also occurred in some nimals. In the quantitative tests, the inimum swelling occurred at ionic strength .4 to 2.0. The variation in size of fibrin lot with drug level and plasma volume and he increased swelling with drug concentraion indicate the major role of both drug evel and medium composition in inflammation. oth the incidence of necrosis and degree of welling are influenced by the use of hyperonic solutions. Using a hyperosmotic soluion of the drug with slightly acid pH dereases inflammation.

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728 Pletscher, A., Kunz, E., Staebler, H., & Gey, K. F. **The uptake of tryptamine by brain in vivo and its alteration by drugs.** Biochemical Pharmacology, 12:1065-1070, 1963.

This study measured the uptake of tryptamine in the brain and heart in vivo, after pretreatment with chlorpromazine (0 to 20 mg per kg), chlorprothixene (10 mg per kg), and chlorisondamine (25 mg per kg), to determine whether the hypothermia induced by these neuroleptics primarily attenuates the activity of reserpine and MAO inhibitors rather than inhibiting the penetration of monoamines. White Wistar rats (60 to 90 g) were fasted 16 hours and then injected with 15 mg per kg of tryptamine i.p. 1 to 2 hours after s.c. administration of the three neuroleptics. Rats used as controls were given the amine only. All animals were given 155 mg per kg of iproniazid phosphate i.p. 12 to 16 hours prior to tryptamine to inhibit MAO. The concentration of tryptamine declined rapidly in the heart and blood but persisted (1 hour) in the brain. The inhibiting effect of chlorpromazine on the tryptamine increase in the brain (but not in the heart) showed time course similar to its hypothermic action. By elevating environmental temperature, book hypothermia and the interference of the drug on tryptamine increase were prevented. The brain, in contrast to the heart, takes up tryptamine by an active mechanism. Its counteraction by the drugs seems to result partly from their hypothermic effect.

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729 Heyman, Jack J. **Nicotinamide metabolism in schizophrenics, drug addicts, and normals: The effect of psychotropic drugs and hormones.** (Paper presented at a meeting of the Section of Biological and Medical Sciences of the New York Academy of Sciences, New York, December 9, 1963.)

In an extension of earlier work (1962), the reactions of 11 schizophrenic women, 4 normal women, 19 male drug addicts, 46 schizophrenic, and 10 normal men to hormones, antidepressants, tranquilizers, and psychotomimetics were studied. The mean N-methyl-2-pyridone-5-carboxamide and N-methylnicotinamide coefficients for the drug-addict group were not significantly different from those of the normal group, but differed from those of the schizophrenic group. The 10th and 20th day mean coefficients of the women subjects were not significantly different, but the N-methyl-2-pyridone-5-carboxamide coefficient of schizophrenics was significantly higher than for normals. All the tranquilizers raised the N-methylnicotinamide coefficient, and with the exception of amitriptyline, all the antidepressants tested raised both coefficients. In laboratory experiments, neither Lactobacillus caseii nor Pseudomonas fluorescens showed reversal of chlorpromazine effects (i.e., less growth; inhibition of oxygen uptake) with the addition of hydrolyzed yeast nucleic acids. Therefore, the evidence to date indicates that the hypothesis that schizophrenia involves, in part, greater oxidative phosphorylation, and that tranquilizers partially block this oxidation, is still tenable.

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730 Denys, Annette, Lévy, Jeanne, & Michel-Ber, Estera. **Mise en évidence, par un test pharmacologique, de relations entre le métabolisme de quelques dérives de la pyridoxine et l'action antidépressive, chez la Souris, d'inhibiteur de la monoamine oxydase (IMAO).** (Demonstration by a pharmacological test, of relations between the metabolism of some pyridoxine derivatives and the antidepressive action, in the mouse, of monoamine oxidase inhibitor (IMAO)). (Paper presented at the meeting of the Academy of Sciences, Paris, November 5, 1962.) Comptes Rendus Hebdomadaires des Seances de l'Academie des Sciences, 255:2528-2530, 1962.

To evaluate the role of pyridoxalphosphokinase in the arousal reaction produced by DOPA in the presence of MAO inhibitors, the effects of i.p. injections of 270 to 300 mg per kg pyridoxal-5-phosphate (P5P), pyridoxal, pyridoxine, pyridoxamine, and pyridoxamine-5-phosphate chlorhydrates were compared. Mice of the Swiss strain were given the pyridoxine derivatives 30 or 60 minutes prior to chloral hydrate, either before (preventive action) or after (therapeutic action) an MAO inhibitor. The hypnotic action of chloral hydrate was blocked by the combination hydrazino-2-octane (D.1514) plus DOPA, but it reappears to different degrees when certain pyridoxine derivatives are added. It was found that P5P is equal to pyridoxal, which is stronger than pyridoxine in blocking the arousal action of DOPA in the presence of an MAO inhibitor, while pyridoxamine and pyridoxamine-5-phosphate are inactive. In regard to therapeutic action, P5P is more effective than pyridoxal, and the other derivatives are ineffective.

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731 Rosell, S. & Axelrod, J. **Relation between blockade of H^3-noradrenaline uptake and pharmacological actions produced by phenothiazine derivatives.** Experientia, 19: 318-319, 1963.

The relation between the blockade of H^3-noradrenaline uptake in rat hearts and the pharmacological actions produced by phenothiazine derivatives was studied using promethazine, promazine, selenopromazine, and chlorpromazine. Phenothiazines have a variety of pharmocological actions including antihistaminic, adrenolytic, and antimotor (sedative) effects. This study was done to see which, if any, of these actions affected the uptake of H^3-noradrenaline. Male rats (135 to 155 g) were given i.m. doses of the drugs (4 mg per kg) 30 minutes before H^3-noradrenaline was given i.v. Two hours later the animals were killed and the hearts removed; the homogenized tissues were assayed for H^3-noradrenaline. Promazine, selenopromazine, and chlorpromazine, which have two pronounced antiadrenaline properties, had pronounced effect on storage of H^3-noradrenaline. Promethazine, which has pronounced antihistaminic action but only slight antimotor and antidrenaline action, had no effect on H^3-noradrenaline uptake; however, selenopromazine has only slight antimotor action, but has a pronounced effect on H^3-noradrenaline uptake. It was concluded that it is the antiadrenaline action of certain phenothiazine derivatives that decreases uptake of H^3-noradrenaline.

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732 Steiner, W. G. & Himwich, H. E. **An electroencephalographic study of the blocking action of selected tranquilizers as a function of terminal methyl amine group.** Biochemical Pharmacology, 12:687-691, 1963.

An EEG study was made in rabbits to determine the blocking action of nine tranquilizers as a function of terminal methylamine groups. The nine compounds represent three types of nuclei (chlorpromazine, imipramine, and amitriptyline) and four types of terminal-amine structure (dimethyl, tertiary amine; desmonomethyl, secondary amine; desdimethyl, primary amine; and piperazinyl). Forty-five adult male New Zealand albino rabbits, from 2 to 3 kg, were used. The animals were tracheotomized uder ether and local tetracaine anesthesia, curarized, and artificially respired prior to administration of the drugs. The drugs were administered by femoral vein at the rate of 1.0 mg per kg every 4 minutes until death. Monopolar EEG recordings were obtained from the anterior and posterior cortex, caudate nucleus, thalamus, hippocampus, amygdala, and the reticular substance just cephalad to the pons. Desmonomethyl compounds act rapidly in depressing the EEG-alerting response to handclap, but are not so potent as dimethyl compounds in depressing the EEG alerting evoked by pain. The desdimethyl ending was the least active, being relatively ineffective in modifying the EEG alerting produced by peripheral stimuli. The piperazinyl structure resembled the dimethyl structure when attached to the chlorpromazine nucleus, but it may be more similar to the desdimethyl structure when attached to other nucleus types. It is concluded that variations in drug activity, as measured by block of EEG alerting, are associated with modifications in the terminal structure of the side chain.

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733 Leusen, I., Thoenen, H., & Lacroix, E. **L'iproniazide et l'hypersécrétion gastrique postresérpinique. (Iproniazid and post-reserpine gastric hypersecretion).** Archives Internationales de Pharmacodynamie et de Therapie, 141(1-2):190-198, 1963.

The influence of reserpine on the gastric secretion of dogs and guinea pigs was

udied. Dogs weighing 6 to 14 kg and fitd with Pavlov gastric cannulas were fasted r 14 hours. Following i.v. administration 0.06 mg per kg of reserpine, the gastric cretion was controlled for 2 hours. Subtaneous administration of 100 mg per kg of roniazid 6 to 8 hours before reserpine did t alter gastric secretion. Tetrabenazine s substituted for reserpine in some anils. Experimental guinea pigs weighing 400 800 g were fasted for 48 hours. Of these, e-third were given no treatment, one-third re given 1 mg per kg of reserpine i.p., d one-third received 50 mg per kg of iproiazid i.p. 15 hours before administration reserpine. The dogs showed hypersecreion and hyperacidity of gastric juices imediately after administration of reserpine. reliminary administration of iproniazid roduced no modification of this stimulus. he action of tetrabenazine was similar to hat of reserpine, although much shorter, nd secretion returned to normal within 1 our. Five hours after receiving reserpine, he guinea pigs showed total acidity, espeially free acidity, greatly increased over hose of the control animals. The volume of ecretion relative to body weight did not hange significantly.

aboratoires de Physiologie Normale et athologique de l'Université de Gand, France

734 Kaul, C. L. & Lewis, J. J. **The effects of reserpine and some related compounds upon the levels of adenine nucleotides, creatine phosphate and inorganic phosphate in the rat brain in vivo.** Journal of Pharmacology and Experimental Therapeutics, 140(1):111-116, 1963.

The effects of reserpine, deserpidine, methoserpidine, syrosingopine, methyl reserpate, reserpic acid hydrochloride, and tetrabenazine on the levels of adenine nucleotides, creatine phosphate, and inorganic phosphate in the rat brain frozen in situ were studied to determine if changes in brain adenine nucleotides could be correlated with sedation and with recorded changes in brain catecholamines and indolealkylamines. Male Wister rats, weighing 70 to 95 g, were injected i.p. with varying doses of the drug. The brain was frozen by total immersion of the rat in liquid nitrogen. Extraction and assay procedures were designed to minimize breakdown of labile phosphate esters and to give values as near as possible to those likely to be present in vivo. There were no significant changes in levels of creatine phosphate, adenosine monophosphate, or the total adenine nucleotide pool with any of the drugs. The nonsedative compounds, methoserpidine, reserpic acid, and methyl reserpate, were not active, but the sedative compounds, reserpine, syrosingopine, and tetrabenazine, decreased the adenosine triphosphate (ATP) to adenosine diphosphate (ADP) ratio. This effect was due to a fall in ATP and an increase in ADP values. Although deserpidine caused reserpine-like sedation at a dose of 5 mg per kg, it did not produce a significant fall in ATP. Correlation of ATP levels with levels of catecholamines, indolealkylamines, and acetylcholine has not yet been shown.

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735 Baird, J. R. C. & Lewis, J. J. **Effects of drugs on noradrenaline and 3-hydroxytyramine (dopamine) levels and on the noradrenaline to dopamine ratio in the rat brain.** Biochemical Pharmacology, 12: 579-581, 1963.

Tests were run to determine whether the central-nervous-system effects of amphetamine and some related compounds could be correlated with their effects on noradrenaline and 3-hydroxytyramine (dopamine) levels in the rat brain. Drugs investigated were l-ephedrine hydrochloride, d-amphetamine sulfate, l-amphetamine sulfate, d-methylamphetamine hydrochloride, and optically inactive phenmetrazine hydrochloride. Administration of d-amphetamine (5 and 10 mg per kg) and l-ephedrine (20 and 40 mg per kg) produced falls in the noradrenaline level; none of the drugs produced a change in dopamine level. Injection of d-amphetamine (5 and 10 mg per kg) produced a fall in the noradrenaline-to-dopamine ratio. The effect of l-ephedrine (40 mg per kg) and optically inactive phenmetrazine (1.8 mg per kg) was a fall in total amount of noradrenaline and dopamine; none of the other drugs changed total amine content. Taking the effect on noradrenaline level in rat brain as an indication of potency, d-amphetamine > l-ephedrine > l-amphetamine. The position of the other two drugs is difficult to assess since only one dose level was used. Results on the relative potency of the drugs agree with results from a previous experiment in which the central stimulant activity of various sympathomimetic amines was studied by measuring the increase in spontaneous activity they produced in mine.

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736 Lewis, J. J., Martin-Smith, M., Muir, T. C., Nanjappa, S. N., & Reid, S. T. **Benzo[b]thiophene derivatives. IV. The preparation and pharmacological activity of compounds related to serotonin and gramine.** Journal of Medicinal Chemistry, 6:711-716, 1963.

Seventeen derivatives of benzo[b]thiophene related to serotonin and gramine were prepared and tested for pharmacological activity. Chemical structure, properties, and method of preparation are listed for each compound. The pharmacology of the compounds was tested by the following seven methods: rat uterus; rat--fundus strip; guinea-pig ileum; isolated, perfused, rat hindquarters; isolated rat jejinum; blood pressure of the anesthetized cat and rat; and toxic effects on mice. Each method is described, and results are discussed. Antihistamine, anti-acetylcholine, antiserotonin, and, in some cases, spasmogenic properties were demonstrated. The replacement of the indole-ring system by the benzo[b]thiophene system in these compounds leads to a reduction in agonistic activity and to the emergence of variable, nonspecific antagonistic properties to serotonin, acetylcholine, and histamine.

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737 Kaul, C. L. & Lewis, J. J. Effects of **minor tranquillizers on brain phosphate levels in vivo.** Biochemical Pharmacology, 12(11):1279-1282, 1963.

The effects of diphenylmethane derivatives (azacyclonol and hydroxyzine), chlordiazepoxide, and meprobamate on levels of adenine nucleotides, phosphocreatine, and inorganic phosphate in the rat brain in vivo were investigated. Two stimulants, chemically related to the diphenylmethane derivatives, benactylzine and pipradrol, and 1-(2'-tetrahydrofuryl)-1-ethylamino-2-phenylethane (WIN-19583-4) were also studied. There was no significant effect by any of the drugs on levels of adenosine monophosphate, inorganic phosphate, phosphocreatine, or total adenine nucleotides. The tranquilizers azacyclonol, hydroxyzine, and chlordiazepoxide all lowered adenosine triphosphate (ATP) and raised adenosine diphosphate (ADP) levels, causing the ATP/ADP ratio to fall. At 200 mg per kg, meprobamate caused complete paralysis, but no change in ATP/ADP ratio. At 60 mg per kg, chlordiazepoxide caused depression and paralysis, and a significant fall in ATP/ADP ratio. The stimulants had a reverse effect on ATP/ADP ratio. Pipradrol and benactyzine both caused increased activity. Pipradrol did not increase the ATP level until 40 mg per kg were used, but 40 mg per kg benactyzine caused a significant rise in ATP and a fall in ADP. WIN-19583-4 caused no changes in behavior or adenine nucleotide levels.

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738 Aprison, M. H. & Hingtgen, J. N. **Brain norepinephrine in pigeons during period of atypical behavior following 5-hydroxytryptophan administration.** (Abstract) Federation Proceedings, 22:273, 1963.

Administration of 50 mg per kg d, l 5-hydroxytryptophane hydrate (5HTP) to trained pigeons resulted in depressed behavior. The 5HT content increased fourfold in the telencephalon (T) and diencephalon (D), then declined to normal values over the same time course the behavior followed in returning to normal. Since 5HTP decarboxylase and DOPA decarboxylase are thought to be identical, it was imperative to measure norepinephrine in brain parts and liver during period of atypical behavior. Norepinephrine content in T decreased only near the end of the behavioral effect; in D, it remained unchanged; in the medulla-pons, it was lowered during the complete period; and in the cerebellum, it rose slightly. Liver norepinephrine was elevated. Other trained pigeons were injected with α-methyl m-tyrosine, which is known to unequally deplete brain 5HT and norepinephrine. Decreased behavioral response rates correlated with lowered total brain 5HT (probably increased free 5HT) rather than norepinephrine. (Author abstract, edited)

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739 Davey, M. J., Farmer, J. B., & Reinert, H. **The effects of nialamide on adrenergic functions.** British Journal of Pharmacology, 20(1):121-134, 1963.

A hypothesis was proposed that nialamide diminishes the availability of transmitter as a consequence of a decreased reentry of noradrenaline into a storage site in nerve endings, and that such a decrease in the availability of noradrenaline in hyperactive nerve pathways may account for the antihypertensive effects of monoamine oxidase inhibitors in man. Results from seven experimental situations are discussed: (1) effects of nialamide on the response of blood pressure in

ts to noradrenaline; (2) effect of niala-
de on the action of tyramine in cats pre-
ously treated with reserpine; (3) action
nialamide on the effects of tyramine on
e cat's blood pressure and nictitating
mbrane; (4) effects of nialamide and tyra-
ne on the concentration of noradrenaline
guinea-pig hearts; (5) acute effect of
alamide on the isolated, cross-perfused cat
leen; (6) chronic effects of nialamide on
e isolated, cross-perfused cat spleen; and
) effects of nialamide on the concentration
the cat. The results support the hypoth-
sis that nialamide diminishes the avail-
ility of transmitter by decreasing reentry
noradrenaline into a storage site in nerve
ndings that is of limited capacity for up-
ake.

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40 Brune, Guenter G., Kohl, Herbert H., Steiner, William G., & Himwich, Harold . **Relevance of the N,N-dimethyl cenfigu-ation of the pharmacological action of hlorpromazine.** Biochemical Pharmacology, 2:679-685, 1963.

quimolar dosages of chlorpromazine (terti-ry amine), desmonomethyl chlorpromazine secondary amine), and desdimethyl chlor-promazine (primary amine), dissolved in olyethylene glycol 400, were administered ntraperitoneally to 81 male albino Wistar ats, and behavior was observed at 90-minute ntervals. Chlorpromazine was found to be two to three times more potent than desmono-methyl chlorpromazine, based on brain pheno-thiazine concentration, in depressing behav-ioral reactivity; desdimethyl chlorpromazine was the least active of the three. Spectro-photometric determination of the concentra-tion of brain phenothiazine, extracted by a modification of the method of Salzman and Brodie, showed identical curves for the three compounds. The relative potency of the drugs in raising thresholds for maximal EEG recruitment and blocking of EEG-alerting response to pain was investigated in 30 male albino New Zealand rabbits. Chlorpromazine was the most potent agent for both effects, followed in decreasing order by desmono-methyl chlorpromazine and desdimethyl chlor-promazine. Desdimethyl chlorpromazine has a relatively high toxicity and death usually occurred at brain phenothiazine concentra-tions of 0.12 to 0.15 micromole per g brain tissue. Progressive demethylation of chlor-promazine decreases its potency of action and increases its toxicity.

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741 Davis, W. Martin. **Neurophysiological basis and pharmacological modification of inhibitory emotional behavior in the rab-bit.** Archives Internationales de Pharmaco-dynamie et de Therapie, 142(3-4):349-360, 1963.

A hypothesis is presented concerning the functional interaction of the reticular acti-vating system, the thalamic "intralaminary synchronizing recruiting system," and the limbic system in the occurrence of an aki-netic inhibitory state (paroxysmal inhibi-tion, animal hypnosis, or tonic immobility). Paroxysmal inhibition was induced in New Zealand white rabbits, 2 to 4 kg, of both sexes. The average duration of immobility on five positive trials (animals remained supine for 10 seconds) was taken as a mea-sure of predrug responsiveness, and the av-erage of two positive trials was taken as the postdrug measure. Drug or control solu-tions, in doses from 0.1 to 1.0 cc per kg, were injected i.v., and immobilization trials were conducted at 10, 30, 60, 90, and 120 minutes after injection. Drugs tested in-clude morphine hydrochloride, levallorphan tartrate, chlorpromazine, hydrochloride, me-probamate, carisoprodol, dimethylamino-ethanol, ethylmethylaminoethanol, d-amphet-amine sulfate, and sodium pentobarbital. Reduction of hippocampal excitability, re-duction of recruiting activity, or enhance-ment of ascending reticular activity are characteristics of antagonists of the inhib-itory response (levallorphan, d-amphetamine, meprobamate), while converse effects are characteristics of synergists (morphine, chlorpromazine, pentobarbital, deanol, ethyl-methylaminoethanol). The possible signifi-cance of this induced inhibition as an ex-perimental model of inhibitory psychiatric reactions is considered.

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742 Lewis, J. J. & Van Petten, G. R. **The effect of antidepressive drugs and some related compounds on the levels of ade-nine nucleotides, inorganic phosphate and phosphocreatine in the rat brain.** British Journal of Pharmacology and Chemotherapy, 20(3):462-470, 1963.

The effects of iproniazid, isoniazid, phenelzine, tranylcypromine, harmine, imipramine, amitriptyline, orphenadrine, diphenhydramine, and cocaine on the levels of adenine nucleotides, inorganic phosphate, and phosphocreatine in the rat brain have been studied. Male Wistar rats, 75 to 95 g, were injected i.p. with varying doses of the drugs. Rats were divided into groups of three, each of equal weight; one rat received a control solution, and two received drug. The animals were killed at varying times after injection, their brains were frozen, and brain levels of adenine nucleotides, inorganic phosphate, and phosphocreatine were determined. With the exception of harmine and diphenhydramine, each of these compounds increased the brain level of adenosine triphosphate and, with the exception of imipramine and cocaine, the level of adenosine diphosphate decreased. Harmine had no effect on levels of adenine nucleotides and, in the case of diphenhydramine, the level of adenosine diphosphate increased, and the level of adenosine triphosphate tended to decrease. There appears to be a relationship between the ability of the drugs to cause behavioral signs of central nervous stimulation and to produce an increase in the adenosine triphosphate—diphosphate ratio. This effect may be a factor in the action of antidepressive drugs.

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743 Janssen, Paul A. J., Niemegeers, Carlos J. E., Schellekens, Karel H. L., Verbruggen, Frank J., & Van Nueten, Jan M. **The pharmacology of dehydrobenzperidol, a new potent and short acting neuroleptic agent chemically related to haloperidol.** Arzneimittel-Forschung, 13:205-211, 1963.

Detailed pharmacological experiments were conducted with rats, mice, cats, dogs, and monkeys, comparing dehydrobenzperidol, a new butyrophenone derivative chemically related to haloperidol, with chlorpromazine, haloperidol, and other neuroleptics. The pharmacological profile of the new drug shows that it acts faster and for relatively shorter time than most other neuroleptics tested; it is relatively atoxic, and because it is active at very low dose levels, it has a great margin of safety; it produces fewer symptoms of excitomotor agitation than the other neuroleptics tested; it is an extremely potent and specific antishock agent, and is about 1,000 times more active than chlorpromazine in blocking the emetic effects of apomorphine.

Research Laboratories
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744 Gala, Richard R. & Reece, Ralph P. **Effect of a reserpine analogue, methyl-18-epi-o-methyl-reserpate hydrochloride, on lactogen release from rat anterior pituitary.** Endocrinology, 72:649-657, 1963.

Studies on the estrous cycle of hooded Norway rats revealed a prolongation of the cycle from 4.8 days for controls to 11.6 days for animals injected with 2 mg per kg, s.c., of the reserpine analog methyl-18-epi-o-methyl-reserpate hydrochloride (SU-9064). The positive deciduomata response seen in a later experiment indicated that the prolongation response was due to the ability of SU-9064 to stimulate progesterone production from the corpus luteum of the cyclic rat. Observations on mammary glands indicate that SU-9064 stimulates gland growth and initiates secretory activity. Lactating mothers isolated from their litters and given either 2 or 5 mg per kg of SU-9064 showed an 11.4% and a 24.2% decrease, respectively, in anterior pituitary lactogen. This finding suggests that the lactogen-releasing ability of reserpine and its analog resides in that part of the molecule common to both compounds.

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745 Ritchie, J. M. & Armett, Christine J. **On the role of acetylcholine in conduction in mammalian nonmyelinated nerve fibers.** Journal of Pharmacology, 139:201-207, 1963.

Desheathed bundles of nonmyelinated nerve fibers (C fibers) from the rabbit vagus nerve and the hypogastric nerve were studied. Both the action potential and changes in the resting potential were recorded by the sucrose-gap method of Stampfli and Straub. The drugs tested were dibucaine hydrochloride, morphine hydrochloride, morphine sulfate, nalorphine sulfate, prostigmine bromide, prostigmine chloride, hexamethonium chloride, and tubocurarine chloride. Neither hexamethonium nor prostigmine in concentrations up to 50 millimoles block conduction in the nerve fibers, but the evidence suggests that they are able to reach and antagonize acetylcholine at receptors in the nerve membrane when applied in much lower concentrations. A high concentration of morphine hydrochloride (5 millimoles) reversibly reduces the depolarization produced by acetylcholine. The same concentration of nalorphine also reduced this depolarization. Dibucaine (1 millimole) abolished both the action potential and the response to acetylcholine for several hours.

ne of the other compounds that inhibited e action of acetylcholine had any marked fect on the action potential. The evi- nce does not support the theory of a phy- ological role of acetylcholine in axonal nduction.

bert Einstein College of Medicine w York, New York

46 Huang, T. F. Studies on prevention and abolition of fibrillation of the at's heart by drugs. Archives Internationales de Pharmacodynamie et de Therapie, 41(1-2):239-253, 1963.

ne coronary artery was ligated in situ in 10 cats. Test drugs were given i.v. 10 to 5 minutes before ligation. By using χ-quare analyses, the incidence of ventricular fibrillation within 10 minutes after igation was compared between the experimental and control groups. Fibrillation was roduced in situ as follows: control group, 0%; none in quinidine sulfate (7mg/kg), rocaine hydrochloride (6.6 mg/kg), hydroxy- ine hydrochloride (5.2 mg/kg), and mecli- ine hydrochloride (7 mg/kg); reserpine 0.27 mg/kg), 30%; chlorpromazine (4.3 mg/kg), 0%; perphenazine (9.3 mg/kg), 20%; niaci- amide (238 mg/kg), 30%; sodium succinate 227 mg/kg), 20%; and prednisolone (2.18 g/kg), 20%. The following drugs given i.v. abolished auricular fibrillation induced by Sherf's method in 5 cats: quinidine sulfate (1.3 mg/kg), procaine hydrochloride (5.28 mg/kg), hydroxyzine hydrochloride (4.8 mg/kg), meclizine hydrochloride (15 mg/kg), and benedryl (10 mg/kg). Ineffective in this experiment were reserpine (0.2 mg/kg), chlorpromazine (1 mg/kg), perphenazine (2 mg/kg), niacinamide (250 mg/kg), sodium succinate (250 mg/kg), and prednisolone (2.5 mg/kg). On the isolated cat auricle, quinidine sulfate (2 to 5 mg/50 ml bath fluid) restored regular rhythm within 15 minutes. Also effective were procaine hydrochloride (2 to 10 mg/50 ml bath), hydroxyzine hydrochloride (2 to 3 mg/50 ml bath), and atropine (0.1 to 1.0 mg/50 ml bath). Meclizine hydrochloride was not tested in this experiment. In other experiments, quinadine sulfate, procaine hydrochloride, and hydroxyzine hydrochloride lengthened the refractory period of the cat atria in vitro, diminished or reversed the adrenaline response of the cat's blood pressure, and prevented and abolished the antiveratrinic action as tested in vitro on the sartorius muscle of the toad. Chlorpromazine was also effective in the latter.

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747 Nayler, Winifred G. A direct effect of reserpine on ventricular contractility. Journal of Pharmacology and Experimental Therapeutics, 139:222-229, 1963.

The direct action of reserpine on isolated toad ventricular muscle was studied. The ventricular muscle was dissected from unselected pithed toads (Bufo marinus) of either sex. For isometric studies, strips of ventricular muscle (about 15 x 1.5 mm) were immersed in a 30-ml Ringer solution bath, and a resting tension of 2.5 g was applied. The strips were stimulated with supramaximal, 10-millisecond pulses at the rate of 6 pulses per minute, as was the isotonic study. In a series of 30 equilibrated preparations stimulated throughout at 6 pulses per minute, isotonic contractions were recorded both before and after the addition of reserpine to give a final concentration of 1.0μg to 5.0μg per ml. A positive inotropic response occurred in the isolated toad ventricle when reserpine of 1μg per ml was added. Larger doses of reserpine (1.5μg to 5μg per ml) evoked a negative inotropic response. This latter response could be reversed by administering caffeine, strophanthin-G, or additional Ca^{++}. Reserpine-treated ventricles showed a reversed staircase phenomenon, and poststimulation potentiation was absent. These changes were associated with an altered efflux of Ca^{45}. The possible relationship between the ability of reserpine to release catecholamine stores and the altered Ca^{45} efflux induced by reserpine is discussed along with the possible significance of the reserpine-induced decline in ventricular contractility.

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748 Cossa, P., Darcourt, G., & Gagnière, B. Sur un effet de potentialisation très particulier du carbamate de propyncyclohexanol (Mérinax) dans les cures de sommeil. (A particular potentiation effect of propynylcyclohexanol carbamate in sleep therapy). Annales Medico-Psychologiques, 120:973-974, 1962.

Nine patients taking a course of sleep therapy developed a syndrome as a side effect of drug therapy. These patients had begun the therapy with daily doses of promethazine (75 mg), chlorpromazine (75 mg), iso-amyl-ethyl-malonylurea (300 mg), and secobarbital (300 mg). Since these doses did not insure sufficient sleep, additional daily doses of carbamate of propynylcyclohexanol (800 mg to three patients and 1,200 mg to

the others) were given. After 5 days of treatment, the patients presented the following syndrome: (1) a deep coma; (2) a special agitation consisting of rotation in bed and falling out of bed, and (3) copious diarrhea. This state lasted 10 to 20 hours. The syndrome has been observed only after administration of carbamate of propynylcyclohexanol, and the syndrome is attributed to a potentiating effect of this product.

(No address)

749 Fraser, H. F. & Rosenberg, D. E. **Observations on the human pharmacology and addictiveness of methotrimeprazine.** Clinical Pharmacology and Therapeutics, 4(5):596-601, 1963.

Methotrimeprazine, a derivative of chlorpromazine, was tested by three methods to evaluate addictiveness in former opiate addicts. The effects of single doses of 8 and 16 mg of methotrimeprazine s.c. were compared with those of 15 and 30 mg of morphine sulfate in a double-blind crossover experiment on 12 male subjects. No morphine-like effects were induced. Methotrimeprazine and a placebo were given s.c. in place of morphine in eight patients stabilized on 240 mg of morphine daily. Doses of 48 mg per day of methotrimeprazine were given to six patients, and 32 mg per day of the drug were given to two patients. The drug did not suppress the signs of abstinence significantly. Two types of the "direct addiction" method were attempted in which methotrimeprazine was given in progressively increasing doses as tolerated (or accepted) for 18 days or more. This was followed by abrupt withdrawal to ascertain whether physical dependence had developed. Effects of chronic administration were unpleasant, and physical dependence was not induced. It was concluded that methotrimeprazine does not possess morphine-like addictiveness. Side effects include sedation and postural hypotension. Rectal temperature, respiratory rate, and systolic blood pressure (horizontal) were not affected by the drug, and no extrapyramidal symptoms were noted.

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750 Bircher, R., Kanai, T., & Wang, S. C. **Action of anticonvulsants (pentobarbital, trimethadione and 3-methyl-5, 5-phenylethyl hydantoin) on the EEG and blood pressure changes induced by pentylenetetrazol, picrotoxin and deslanoside in dogs.** Archives Internationales de Pharmacodynamie et de Therapie, 141(3-4):357-376, 1963.

The protective effects of the anticonvulsants, pentobarbital, trimethadione, and 3-methyl-5,5-phenylethyl hydantoin on EEG convulsive discharges, ECG changes, and blood-pressure changes induced by the convulsants, pentylenetetrazol, picrotoxin, and deslanoside, were investigated in dogs. Optimal doses of the anticonvulsants were determined for production of convulsive discharge and/or cardiac arrhythmias and vasopressor effects. The anticonvulsants were administered i.v. or into the ventricles of the brain. For intraventricular administration, cannulae were chronically implanted in the lateral and fourth ventricles of the dog. Doses of 36 mg per kg i.v. pentobarbital, 300 to 500 mg per kg i.v. trimethadione, and 100 mg per kg i.v. or i.p. 3-methyl-5,5-phenylethyl hydantoin protected against the reversible EEG convulsive discharges produced by effective doses of pentylemetetrazol or picrotoxin, i.v. or into the brain ventricles. Temporary protection was given against reversible EEG convulsive discharges produced by deslanoside injected into the brain ventricles, but not against the lethal effect of the drug, which occurred 5 to 72 hours later. The anticonvulsants protected against ECG cardiac arrhythmias produced by pentylenetetrazon and picrotoxin. They were also effective in preventing cardiac arrhythmias induced by intraventricular, but not intravenous, deslanoside. The anticonvulsants did not fully protect against vasomotor stimulation evoked by the convulsants.

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751 Dandiya, P. C. **Studies on central nervous system depressants (II). The action of some general nervous depressants on coaxically stimulated guineapig's ileum.** Archives Internationales de Pharmacodynamie et de Therapie, 141(1-2):216-222, 1963.

The effect of seven central nervous system depressants, reserpine, chlorpromazine, prochlorperazine, azacyclonol, hydroxyzine, 2-p-chlorophenyl-3 methyl-2,3 butanediol, and meprobamate, was studied on the twitch of guinea pig ileum caused by electrical stimulation. The action of the depressants was compared to that of morphine and codeine to localize the mechanism of action. Isolated small intestine was suspended in an aerated bath of Kreb's solution, and muscle reactions to the addition of less than 1 ml of the test drugs to the bath were recorded on a smoked drum. Current pulses of 1 millisecond duration and 4 volts were applied to electrodes attached to the intestine at 15-second intervals. Acetylcholine was also

ded to the bath to induce muscle contraction; if pretreatment with test drugs prented response to control doses of acetylholine, higher doses were tried. All of he drugs but meprobamate and 2-p-chlorohenyl-3 methyl-2,3 butanediol, a new tranilizing agent, depressed the action on the leum section. Muscle twitch was reduced to decreasing extent in morphine, codeine, eserpine, and chlorpromazine; twitch was estored partially by acetylcholine. Muscle vitch was completely blocked and could not e restored by acetylcholine when 1 mg prohlorperazine, 1 mg azacyclonol, or 1 mg ydroxyzine were added to the bath.

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52 Goldberg, M. E., Johnson, H. E., Knaak, J. B., & Smyth, H. F., Jr. **sychopharmacological and biochemical effects f n-methyl 3-isopropyl phenyl carbamate Compound 10854).** (Abstract) Federation roceedings, 22:510, 1963.

-methyl 3-isopropyl phenyl carbamate was ound to be a potent inhibitor of acetylholinesterase. Threshold effects in rats xposed by inhalation to 45 mg per cubic eter of the compound or injected i.p. were ssociated with inhibition of 40% to 50% of rain cholinesterase. Administration of 1 g per kg of the compound produced behavoral changes that persisted for 60 to 75 inutes; brain cholinesterase levels returned to normal after 2 hours. Pretreatent with 0.5 mg per kg of atroprine abolished behavioral effects. Barbiturate potenciation in mice was obtained after i.p. injection of 1.6 mg per kg.

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753 Setnikar, Ivo, Murmann, Walter, & Magistretti, Maria J. **Analysis of the antagonism between some brain stem stimulants and pentobarbital.** Archives Internationales de Pharmacodynamie et de Therapie, 141(1-2):199-209, 1963.

Data from a study on mutual antagonism between brain-stem stimulants and pentobarbital were subjected to statistical analysis to see if the antagonism was competitive and reversible. Brain-stem stimulants studied were 2-phenyl-3-methyl-7-methoxy-8-dimethylaminomethyl-chromone hydrochloride, 2,3-dimethyl-7-methoxy-8-morpholinomethyl-chromone hydrochloride, bemergride, pentetrazole, and picrotoxin. Equations were derived to quantitatively analyze the antagonism of brain-stem stimulants against the toxic effects of pentobarbital; these same equations were converted to analyze the antagonism of pentobarbital against the toxic effects of brain-stem stimulants. It was concluded that the antagonism was not competitive. The conclusion is valid if the competitive antagonism is based on a reversible chemical combination, regulated by the law of mass action and of the agonist and antagonist drugs with the "receptors" in the brain, the latter having the characteristics of chemical functions. The same conclusion is valid if the antagonism is based on phenomena of isothermal adsorption or simply on a statistical basis, irrespective of the chemicophysical phenomena involved in the action of the agonist drug and in the counteraction of the antagonist drug.

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754 White, Richard P. & Carlton, Robert A. **Evidence indicating central atropine-like actions of psychotogenic piperidyl benzilates.** Psychopharmacologia, 4:459-471, 1963.

Piperidolate hydrochloride (JB 305), mepenzolate bromide (JB 340), 1-ethyl-3-piperidyl phenylcyclopentylglycolate hydrochloride and 1-ethyl-2-pyrrolidylmethyl phenylcyclopentylglycolate hydrochloride (JB 329), and 1-ethyl-3-piperidyl benzilate hydrochloride (JB 318) were injected into 108 rabbits of both sexes, weighing 1.7 to 3.4 kg, via an indwelling catheter inserted into the saphe-neous vein. The EEG's were obtained from steel electrodes inserted into different parts of the brain. Eight unrestrained rabbits were observed only for behavioral effects of the experimental drugs. In adequate doses, each of the JB compounds induced EEG synchrony and blocked the EEG effects of exteroceptive stimuli. In this, JB 329 was more effective than JB 318, and both were approximately 200 times more potent than JB 305 and 800 times more potent than JB 340. In the case of JB 340, lower doses often exerted as much effect as the highest dose. The EEG effect of noise was usually abolished first by these drugs, and tactile effects disappeared subsequently, or with higher doses. JB 305 and JB 340 failed to block the EEG effects of 0.1 mg per kg physostigmine. JB 329 and JB 340 produced mydriasis that persisted after administration of physostigmine, but mydriasis produced by JB 318 and JB 305 was counteracted by physostigmine. None of the JB compounds significantly changes the respiratory rate

or reduces muscle tone. No differences were apparent in the effects on EEG of the JB compounds in rabbits and in curarized cats. All four piperidyl benzilates blocked the EEG effects of amphetamine, but only the psychotogenic agents, JB 329 and JB 318, blocked EEG activation by physostigmine. This suggests that these compounds may induce hallucinogenic phenomena by central anticholinergic mechanisms.

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755 Camplo, J. & Torrubia, H. **A propos de l'action du 20-28 M.D. (The action of 20-28 M.D.)** Annales Medico Psychologiques, 2(1):146-147, 1962.

In connection with clinical testing of 20-28 M.D. on 50 patients and a study of certain environmental reactions in the neuroleptic syndrome, the authors insist that all therapy tends to modify an existing relational system by facilitating certain exchanges and rejecting others, and by mobilizing an entire series of affective currents. In estimating the action of a drug, consideration must be given not only to the pharmacodynamic effects on the patient, but also to the counter-reactions of the environment. Thus the concept of "secondary effect" must not stop merely with determination of neuroleptic impregnation.

(No address)

756 Akers, Thomas K. & Peiss, Clarence N. **Comparative study of effect of epinephrine and norepinephrine on cardiovascular system of turtle, alligator, chicken and opossum.** Proceedings of the Society for Experimental Biology and Medicine, 112:396-399, 1963.

Turtles, alligators, opossums, and chickens were given epinephrine and norepinephrine i.v., and their cardiovascular responses were compared. All the animals were anesthetized with chloral derivatives. Both epinephrine and norepinephrine significantly or moderately increased diastolic pressure in all test animals. Epinephrine affected the heart ratio and pulse pressure in all the species, and norepinephrine had this effect in the turtle and alligator. Total duration of responses was much longer in the alligator than in the higher animals, although much shorter than in the turtle. Total duration of response for epinephrine was 30 seconds in the opossum and 60 to 80 seconds in the chicken compared to 200 seconds and 23 to 40 seconds, respectively, for norepinephrine. It may be concluded that both catecholamines increase the initial velocity of myocardial contraction, with a greater extent of increase shown by epinephrine. A tentative hypothesis that epinephrine is the neurotransmitter in the opossum and norepinephrine is the neurotransmitter in the chicken, is considered.

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757 Varma, D. R., Gillis, R. A., & Melville, K. I. **On the relationship of catecholamines and thyroid activity to ventricular fibrillation during hypothermia in dogs.** Canadian Journal of Biochemistry and Physiology, 41:361-367, 1963.

The possible significance of endogenous catecholamines in the production of hypothermic ventricular fibrillation was investigated. Ventricular fibrillation was produced by coronary occlusion of adult mongrel dogs anesthetized with i.v. pentobarbitone sodium, under artificial respiration and in a condition of hypothermia. Before hypothermia, dogs were pretreated with iproniazid (200 mg per kg, i.v.), phenoxybenzamine (15 mg per kg, i.v.), or reserpine (0.5 mg per kg, i.v.). To assess the importance of thyroid function, one group of dogs was thyroidectomized, and another group was injected with methimazole. It was observed that reserpine treatment, thyroidectomy, and antithyroid treatment markedly decreased the occurrence of ventricular fibrillation, but iproniazid and phenoxybenzamine were completely ineffective in reducing its incidence. The protective action of reserpine was counteracted by combined pretreatment with liothyronine sodium. Ventricular fibrillation occurred in only 40% of the reserpine-pretreated dogs. No correlation was found between ventricular catecholamines content and incidence of ventricular fibrillation.

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758 Platz, Arthur, Uhr, Leonard, Clay, Margaret, Miller, James G. & Kristofferson, Alfred B. **Time and dosage effects of meprobamate on visual detection.** Psychopharmacologia, 6:42-48, 1963.

Time and dosage response curves for meprobamate, administered in acute dosages within

e therapeutic range, were traced to see if
e drug affected the threshold of visual
tection. Sixteen male college students,
ed 21 or over, participated in a double-
ind own-control experiment under three dos-
es of meprobamate (400, 800, and 1,600 mg)
d matching dosages of placebo to determine
sponse curves on a visual detection task
er a 4-1/2 hour period, from 5:00 to 9:30
M. To control for possible daily cycle
ffects, two additional runs with 13 of the
bjects under placebo and 1,600 mg meproba-
te were conducted from 8:30 A.M. to 12:30
M. The first 15 minutes of each cycle
onsisted of individually administered psy-
omotor tests and self-report inventories.
he second half of the cycle was used for
hreshold determinations, lasting 12 minutes.
here were seven cycles of threshold deter-
ination: an immediate predrug test, and
est periods beginning at 1/4, 3/4, 1-1/4,
-3/4, 2-3/4, and 3-3/4 hours after inges-
ion. Evening tests showed statistically
ignificant dosage effects, time effects,
nd a significant drug-by-subject interac-
ion. This differential drug effect may be
ependent on the momentary physiological and
sychological state and the diurnal meta-
olic rhythm of the subject.

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759 Rosenberg, D. E., Wolbach, A. B., Jr., Miner, E. J., & Isbell, Harris. **Observations on direct and cross tolerance with LSD and D-amphetamine in man.** Psychopharmacologia, 5:1-15, 1963.

Seven Negroes and three Puerto Ricans, from 25 to 36 years of age, participated in a single-blind, crossover study, covering 68 to 100 days that consisted of 7 periods—testing the drugs in nontolerant subjects (19 to 28 days), chronic administration (13 days), test of direct and cross tolerance (2 days), withdrawal (10 to 14 days), and repetition of the above sequence. The drugs and doses were the following: 0.3 to 1.5 mcg per kg lysergide tartrate, 0.6 mg per kg d-amphetamine, and placebo. Measurements were made of temperature, pulse, blood pressure, pupillary diameter, kneejerk, responses to questionnaire, and clinical grading by a physician. Results showed that, following daily administration for 14 days of 1.5 mcg per kg LSD, direct tolerance develops with respect to pupillary dilatation and mental excitation, and following daily administration for 14 days of 0.6 mg per kg d-amphetamine, direct tolerance develops with respect to temperature elevation, systolic blood-pressure increase, and mental excitation. Subjects directly tolerant to LSD are not cross tolerant to d-amphetamine, and those directly tolerant to d-amphetamine are not cross tolerant to LSD.

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760 Stefko, P. L. & Zbinden, G. **Effect of chlorpromazine, chlordiazepoxide, diazepam and chlorprothixene on bile flow and intrabiliary pressure in cholecystectomized dogs.** American Journal of Gastroenterology, 39:410-417, 1963.

The effects of chlorpromazine, chlordiazepoxide, diazepam, and chlorprothixene on bile flow and intrabiliary pressure were studied in cholecystectomized dogs. The drugs were given intravenously. Dosages were chlorpromazine, 0.25 to 20 mg per kg; chlordiazepoxide, 4 to 32 mg per kg; diazepam, 0.5 to 16 mg per kg; and chlorprothixene, 4 to 16 mg per kg. Chlorpromazine caused a decrease in bile flow and a marked increase in intraductal pressure at doses as low as 2 mg per kg, whereas chlordiazepoxide and diazepam had no effect up to 16 mg per kg and 8 mg per kg, respectively. Higher doses caused sedation, ataxia, and respiratory depression, and increased biliary pressure was observed at 32 mg per kg chlordiazepoxide and 16 mg per kg diazepam. Chlorprothixene in doses up to 16 mg per kg was without effect on bile flow and intrabiliary pressure. Since intrahepatic cholestasis occurs in patients treated with chlorpromazine, but has not been observed with chlordiazepoxide, diazepam, and chlorprothixene, it is felt that the pharmacological effect on bile flow and intrabiliary pressure may be a contributing factor in chlorpromazine-induced jaundice.

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761 Khazan, N., Ben-David, M., & Sulman, F. G. **ADH-like effect of tranquilizers in amphibians.** Proceedings of the Society for Experimental Biology and Medicine, 112:490-494, 1963.

Seventeen tranquilizers---chlorpromazine, prothixene, phenobarbitone sodium, prothipendyl, butyrylperazine, triflupromazine, hydroxyzine, promethazine, levomepromazine, chlordiazepoxide, meprobamate, trifluoperazine, benactyzine, pipamazine, perphenazine, reserpine, and methopromazine---were studied for the antidiuretic-hormone-releasing effect of inducing increased water uptake and

body weight gain in the amphibians Bufo viridis and Rana pipiens. Both intact and hypophysectomized animals were studied. In intact animals, phenothiazine derivatives produced a varying degree of increased water uptake through the skin. Chlorpromazine was more effective than either exogenous antidiuretic hormone (pitressin) or pituitary homogenates, since it lasted 24 to 48 hours. Phenothiazine derivatives with a Cl-atom at position 2 and a dimethylaminopropyl side-chain at position 10 gave the maximum effects. Chlordiazepoxide, meprobamate, benactyzine, and reserpine showed no effect. In hypophysectomized toads and frogs, chlorpromazine produced a very weak effect. Hypersecretion of antidiuretic hormone from the hypothalamus and from the posterior pituitary can be effected through the action of tranquilizers.

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762 Steiner, J. E. & Sulman, F. G. **Simultaneous studies of blood sugar, behavioural changes and EEG on the wake rabbit after administration of psilocybin.** Archives Internationales de Pharmacodynamie et de Therapie, 145(3-4):301-308, 1963.

A simultaneous investigation of the blood-sugar level, behavioral changes, and corticographic changes after administration of psilocybin was performed on wake rabbits. Psilocybin was given at the optimal dose of 3.5 mg per kg i.v. Blood samples were taken every hour for 6 hours. Criteria for testing behavioral changes were general motor activity, spontaneous food intake, spontaneous drinking, reaction to sonic and photic stimuli, horror reaction, and emotional tension. Electrocorticography was done using a 3-channel Schwarzer EEG-apparatus and permanently implanted epidural electrodes. Blood sugar levels increased 30 to 40 minutes after injection, returning to normal after 5 or 6 hours. Behavioral changes, which began 20 to 30 minutes after injection, included increased water intake, irritability, anxiety, chewing, licking, spontaneous motor activity, and phonation. Corticographic changes noted were decrease of voltage and of cortical potentials, and desynchronization of brain activity. All changes appeared simultaneously. Psilocybin evokes biological responses similar to those of adrenaline, suggesting a possible action on the hypothalamus. Increase in blood sugar suggests that the glycokinetic effect of psilocybin may be related to that of the pressor amines.

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763 Danon, A., Dikstein, S., & Sulman, F. G. **Stimulation of prolactin secretion by perphenazine in pituitary-hypothalamus organ culture.** Proceedings of the Society for Experimental Biology and Medicine, 114:366-368, 1963.

A combined pituitary--hypothalamus organ culture was used to study the mechanism of action of perphenazine, a hypothalamic depressor, on prolactin secretion in vitro. Adult female rats, weighing 200±20 g each, served as donors for the organ cultures; 50 were untreated and 50 were primed with 10 mg per kg perphenazine for 10 days. Organs were cultured on "199" nutrient medium to which 2 units insulin, 200 international units of pen cillin, and 0.1 mg dihydrostreptomycin sulfate per ml were added. Cultures were incubated 7 days at 36° C. Nutrient medium was replaced every day. The collected media were assayed for prolactin. Pituitary explants released an average of 0.05 international units of prolactin daily. Pituitary--hypothalamus co-cultures released only an average of 0.025 international units of prolactin per day. Other brain parts in co-culture failed to depress prolactin release. Hypothalami of perphenazine-primed rats and hypothalami to which perphenazine was added in vitro also failed to depress prolactin release.

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764 Yoshii, N., Hano, K., & Suzuki, Y. **Effect of certain substances isolated from "Matatabi" on the EEG of cat.** Folia Psychiatrica of Neurologica Japonica, 17(4): 335-350, 1963.

The Matatabi plant (Actinidia polygama) is relished by cats, causing them to display the following behaviors: licking, salivation, flamen, rubbing, rolling on the ground, ecstasy, and sleep. Three substances were isolated from the plant, with minimum effective i.v. doses: b-phenylethyl-alcohol 1:1,000; actinidine 1:1,000,000; and Matatabi-lactone 1:10,000. These substances were applied to the oral cavity, causing reflex salivation, as well as salivation similar to that produced by pilocarpine. When applied to the brain or injected into various parts of the brain, each substance had similar effects on blood pressure and electrical activities of the brain, but had no effect on respiration. The tests

ndicated the effect on blood pressure was
f central origin, mediated through the va-
al nerves, and could be abolished by atro-
ine treatment. In the EEG, these substan-
es affected, in the following sequence, the
imbic system, the hypothalamus, reticular
ormation, specific and non specific thala-
ic nuclei, the caudate nucleus, and the
ortex. The tests indicate that the choli-
ergic functions of the test substances on
lood pressure and salivary secretion act
nly through central structures, and are op-
osed by atropine. The EEG changes are not
he alerting, but rather, a drowsy pattern.

epartment of Pharmacology
saka University, Japan

765 Ben-David, M., Menczel, E., & Sulman, F. G. **The hypoglycaemic effect of azacyclonol and its mechanism.** Archives nternationales de Pharmacodynamie et de herapie, 145(3-4):309-321, 1963.

he hypoglycemic effect of azacyclonol was tudied to clarify its mechanism of action n certain cases of psychosis. Experimental yperglycemia was produced in 60 male rab-its, following 18 hours of fasting, by s.c. injection of 1 g per kg glucose, 0.03 mg per kg epinephrine, 0.3 mg per kg glucagon, and 2.5 ml per kg acetone, respectively. One-third of the rabbits were given 40 mg per kg azacyclonol simultaneously; one-third were given the same dosage 1 hour prior to the hyperglycemic agent; and the remainder received only the hyperglycemic agent. The results showed an initial decrease in blood sugar 30 minutes after administration of 10, 20, or 40 mg per kg azacyclonol. Only the animals receiving 1 mg per kg showed lowered blood-sugar level 1 hour after administration. Peak reduction at all dosages occurred during the second hour, and the hyperglycemic effect persisted for about 3 hours. The strongest hypoglycemic effect was obtained when azacyclonol was given before the tolerance tests, completely antagonizing hyperglycemic effects in the case of epinephrine.

Hebrew University
Jerusalem, Israel

766 Aghajanian, George. **The effect of chlorpromazine on respiration of brain mitochondria as a function of metabolic state.** Biochemical Pharmacology, 12: 7-12, 1962.

Mitochondria prepared from a single male rat brain (Wistar strain) was studied during metabolic states 1 through 4 (Chance and Williams classification) and certain transitions between them. Oxygen uptake was followed polarographically with a 120-cycle per second vibrating platinum electrode (Oxygraph). There is a characteristic respiratory rate and rate-limiting substance for each combination of levels of adenosinediphosphate (ADP) and substrate. When 50μM of chlorpromazine is added during state 4, a doubling of the respiratory rate occurs. When ADP is added to a medium containing α-ketoglutarate and malate, making the transition from state 4 to state 3, a 3.6-fold increase in oxygen consumption occurs. In this case, 50μM of chlorpromazine has no inhibitory effect. Respiration is least affected by chlorpromazine during periods of greatest activity (state 3); in fact, concentrations of 50μM or less of the drug have no effect. The presence of excess ADP during state 2 does not interfere with chlorpromazine action. It would appear from these studies that a high rate of electron transport, as reflected by fast respiration, rather than high or low steady-state reduction of the electron carriers, is correlated with insensitivity to the drug.

Yale University School of Medicine
New Haven, Connecticut

767 Chessick, Richard D., Kronholm, Jean, & Maier, George. **Effect of lysergic acid diethylamide (LSD-25) and other drugs on tropical fish.** Journal of Nervous and Mental Disease, 137(4):389-394, 1963.

Thirty species of tropical fish were screened for LSD-25 reactions. Eleven were found to have repeatable behavior changes, but none showed all the behavior changes seen in the responses of Siamese Fighting Fish. A common characteristic shown by all reactors was surface swimming. Since none of the 10 species showing consistently repeatable reactions to LSD-25, besides Siamese Fighting Fish, showed similar reactions to sodium azide or potassium cyanide, and Siamese Fighting Fish reactions only partially overlap, and then only in a limited temperature range, it must be concluded that the behavioral changes seen with LSD-25 cannot be accounted for by assuming that LSD-25 acts mainly like a respiratory enzyme poison, such as sodium azide or potassium cyanide. Reserpine (10μg per ml) was found to be toxic for three species at high temperatures. Neither serotonin (1 mg per ml), norepinephrine (50μg per ml), nor reserpine (10μg per ml) blocked or potentiated the reaction of LSD-25 (1μg per ml) on any of these fish at any temperature. The number

of reactions generally declined with temperature from 35° C (95° F) to 15° C (59° F), except for reactions to sodium azide, where temperature did not have a profound effect. The optimal temperature appeared to be 30° C (86° F) because of the toxicity seen with some drugs at higher temperatures. Biochemical analysis showed that serotonin did enter the fish, and intraperitoneal injection of reserpine produced no changes. (17 references) (Author abstract, edited)

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768 Assael, M., Ben-David, M., Mishkinsky, Y., Steiner, J. E., & Sulman, F. G., **The effect of mescaline on blood sugar, serotonin metabolism, electrical activity of the brain, light stimuli reaction and behavioural pattern in the wake rabbit.** Archives Internationales de Pharmacodynamie et de Therapie, 146(3-4):537-548, 1963.

Blood-sugar levels, urinary 5HIAA excretion, spontaneous electrical activity of the cerebral cortex, evoked potentials to light stimuli, and behavioral patterns were investigated in 20 wake rabbits with implanted permanent epidural electrodes. In the first stage, mescaline sulphate was injected s.c. in doses of 6, 30, and 60 mg per kg. In the second stage, the same doses of mescaline were administered after 25 days of daily priming with 5 mg per kg of iproniazid dihydrochloride injected s.c. The control animals received identical volumes of normal saline. The test parameters were general motor activity, reaction to food offered ad libitum, reaction to drinking water offered ad libitum, reaction to sonic stimuli (20-second whistle), reaction to photic stimuli (light flashed at 1/15 second), horror reaction, and emotional tension. After administration of various doses of mescaline sulphate alone, there was increased general motor activity and emotional tension. The other four parameters did not show significant changes. When mescaline was given after pretreatment with iproniazid, additional findings were clear changes in the spontaneous electrical activity of the cortex and in the pattern of the potentials to light stimuli. The other three parameters were not affected. The changes observed are interpreted as due to stimulation of the hypothalamus.

Hebrew University-Hadassah Medical School
Jerusalem, Israel

769 Pardo, Efrain G., Cato, Jorge, Gijón, Enrique, & Alonso-deFlorida, Francisco. **Influence of several adrenergic drugs on synaptic transmission through the superior cervical and the ciliary ganglia of the cat.** Journal of Pharmacology and Experimental Therapeutics, 139:296-303, 1963.

Experiments were conducted on the blood-circulated ganglia in situ of fasted cats of both sexes, anesthetized by i.v. injection of sodium hexobarbital (35 mg per kg) and sodium barbital (200 mg per kg). There were approximately 90 experiments on the superior cervical ganglion and 30 on the ciliary ganglion. The drugs tested were l-epinephrine hydrochloride, l-norepinephrine hydrochloride, dl-isoproterenol hydrochloride, dl-amphetamine sulfate, l-ephedrine sulfate, l-phenylephrine hydrochloride, and isometheptene hydrochloride. Each animal received only one of the drugs in saline solution as a continuous infusion. Rates of infusion covered a wide range, from 0.02 µg per kg per minute to 8.0 mg per kg per minute, and infusion was maintained for up to 30 minutes, or until almost complete blockade of transmission was obtained. In blockade of transmission, epinephrine was more potent than norepinephrine; both were more potent than isoproterenol; and all of the catecholamines were more potent than amphetamine, ephedrine, phenylephrine, or isometheptene. Very low rates of infusion of the catecholamines frequently produced enhancement of transmission, which could be demonstrated most easily with isoproterenol. No significant differences were found between the sensitivity of the superior cervical ganglion and the ciliary ganglion to either blockade or facilitation by these compounds.

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770 Dagirmanjian, R. **The effects of guanethidine on the norepinephrine content of the hypothalamus in the cat and rat.** (Abstract) Federation Proceedings, 22:273, 1963.

Single i.p. injections of 15 mg per kg guanethidine failed to lower hypothalamic norepinephrine in cats. Daily s.c. injections of 15 mg per kg for 7 days, however, consistently produced a significant decrease in norepinephrine. Attempts to lower the norepinephrine content of the hypothalamus in rats by single s.c. injections of 5 mg per kg or 15 mg per kg, or by chronic daily s.c. injections of 15 mg per kg guanethidine, were unsuccessful.

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abraham, Cambridge, England

71 Haydu, G. G., Noreikar, L., Sankar, D. B., & Sankar, D. V. S. **Short-term ffect of psychotropic drugs on platelets.** rchives of General Psychiatry, 9(5):108-10, 1963.

our psychotropic drugs---chlorpromazine, hlorprothixene, tranylcypromine, and imi-ramine---were tested for their effect on latelet count and platelet uptake of sero-onin in hospitalized psychotic patients. our groups of eight patients were used. hrombocyte counts and the uptake of radio-ctive serotonin by platelet-rich plasma ere recorded before drug administration nd at 4-day intervals after therapy began. hrombocyte count was done by the modified ees and Ecker method. The amount of sero-onin uptake was calculated as the ratio of adioactive counts per minute to the optical ensity of a lysed blood sample. All four rugs increased the thrombocyte count; hlorprothixene produced the greatest in-rease. The thrombocytosis-producing ef-ect of the drugs appeared to function in-ependently of their serotonin-uptake effect n platelets. Chlorpromazine treatment in-reased the relative uptake, but tranylcy-romine decreased it, both significantly.

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ueens Village 27, New York

772 Gómez-Puyou, A., Tuena, M., Guzmán-Garcia, J., & Pẽna, A. **Further studies of the uncoupling action of triamcinolone in rat liver mitochondria.** Biochemical Pharmacology, 12:669-677, 1963.

In fresh mitochondria, triamcinolone stimulates respiration in media free of inorganic phosphate and phosphate acceptors, and depresses the adenosinephosphate, triphosphate, and adenosinediphosphate (ADP-ATP) exchange reaction. The steroid does not affect these reactions in mitochondria aged for 24 to 72 hours at 0° C to 2° C. Upon asing of the mitochondria, the sensitivity of these reactions to triamcinolone is lost at the same time that the ^{32}P-ATP exchange disappears. Azide, oligomycin, and reduction of the respiratory chain inhibit the triamcinolone-stimulated adenosinetriphosphatase activity of fresh mitochondria. These experiments are consistent with the previous hypothesis that triamcinolone uncouples oxidative phosphorylation in the same site as does 2,4 dinitrophenol. However, it was found that triamcinolone promotes mitochondrial swelling, whereas dinitrophenol in identical conditions does not affect this phenomenon. It is probable that the steroid causes a structural change in the mitochondria before functional changes become apparent. (13 references) (Author abstract, edited)

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Universidad Nacional Autonoma de Mexico
Mexico, D. F.

773 Cession-Fossion, A. **La tyramine agit chez le rat comme libérateur de noradrénaline. (Tyramine acts as a noradrenalin liberator in the rat.)** Comptes Rendus, 156:538-540, 1962.

To test whether tyramine and amphetamine may be classed as direct-acting sympathicomimetic amines, rats of 300 g average weight, anesthetized with nembutal, were injected with 0.5 mg tyramine. This raised the arterial pressure by 5 or 6 cm mercury for about 3 minutes. Injection of 0.1µg adrenaline produced hypertension of 2 or 3 cm very briefly. Repeated injections of tyramine resulted in a gradual drop in vasopressor action to one-half the original level at the 12th dose, when the animals had received a total of 15 to 20 mg per kg tyramine. Intravenous injection of 200µg per kg noradrenaline restored the initial effect of tyramine, again decreasing with successive injections. Injection of 0.5 mg per kg amphetamine produces a hypertension of 2 to 3 cm mercury that disappears by the 4th or 5th dose. Intermixing several successive injections of amphetamine to the tyramine series greatly reduces the hypertensive activity of the latter. This gradually returns to normal. Injection of noradrenaline does not affect the vasomotor effects of amphetamine.

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774 Duritz, Gilbert & Truitt, Edward B., Jr. **The role of acetaldehyde in the action of alcohol on brain norepinephrine and serotonin.** (Abstract) Federation Proceedings, 22:272, 1963.

Rats were given alcohol (2 to 4 g per kg, i.p.), acetaldehyde (300 mg per kg, i.p.), and disulfiram (200 mg per kg, p.o., 3 days) in a study of the effect of acetaldehyde on

brain norepinephrine and 5HT. Norepinephrine and 5HT were determined by fluorimetric analysis. The 5HT level decreased only slightly when alcohol was given alone, with disulfiram, or when acetaldehyde was given. Norepinephrine decreased slightly when ethanol was given alone. Norepinephrine dropped markedly when acetaldehyde was administered. Alcohol given to rats pretreated with disulfiram produced a greater drop in norepinephrine. It is concluded that acetaldehyde is responsible for the effects of alcohol on neurogenic amines.

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See also: 590, 596, 620, 623, 626, 637, 668, 678, 679, 682, 776, 779, 786, 787, 796, 798

5 Horita, A. Some biochemical studies on psilocybin and psilogin. Journal Neuropsychiatry, 4:270-273, 1963.

ochemical studies were made on two indo-amines, psilocybin and its 4-hydroxy ana-g, psilocin, that were recently identified the mushroom, Psilocybe mesicana Heim. th in vivo and in vitro, psilocybin is pidly dephosphorylated to psilocin. Incu-tion of psilocybin with rat kidney homo-nates resulted in the rapid formation of a ue-colored product, identified as the pro-ct of psilocin oxidation. The oxidation ocess is catalyzed by the cytochrome c— tochrome oxidase pathway, and appears to ke place at the -OH group on the indole ng. Livers, kidneys, and brains of mice ven 100 mg per kg psilocybin were analyzed r psilocin. Psilocin appeared rapidly in th liver and kidney; appearance was slower the brain. Before sacrifice, the psilocy-in-treated mice had exophthalmus, piloerec-ion, motor incoordination, and depression. was postulated that psilocin is the phar-acologically active agent after psilocybin dministration. Mice pretreated with 8-gly-erophosphate, which competes with psilocy-in for dephosphoralase, and their given silocybin showed less severe behavioral ef-ects and a considerable decrease in amount nd rate of psilocin formation. A relation-hip was established between intensity of NS actions and rate of appearance of psilo-in in the brain.

niversity of Washington School of Medicine eattle, Washington

76 Lewis, J. J., Martin-Smith, M., & Muir, T. C. **Observations upon roles of ether xygen, alkyl group size, number of onium entres and inter-onium distance upon neuro-uscular block in bis- and polyonium com-ounds.** British Journal of Pharmacology and hemotherapy, 20(2):307-318, 1963.

he cumulative dose-response curves obtained ith several polymethylene bis-, tris- and etra-onium salts on the Rana temporaria ectus abdominis muscle were studied to ob-ain both a convenient classification and a heoretical interpretation of the results. ecamethonium iodide (2μmole/ml) was used as the standard agonist. Compounds having a similar agonistic effect were added to the bath, and those with other types of muscle relaxant activity were added 15 minutes before decamethonium. The intrinsic activity, affinity, and affinity relative to decamethonium were found for oxydipentonium and three other compounds (Group 1). The inhibition index, affinity, and affinity relative to tubocurarine dimethyl ether were found for a group of four ethers (Group 2a), and for another group of eight ethers, including tubocurarine (Group 2b). There were no significant differences in the intrinsic activity values of decamethonium, oxydipentonium, and Compound II, but there were significant differences in these values between decamethonium and Compounds I and III, all compounds being in Group 1. The dose-response curves for Compound I indicated both agonistic and noncompetitive antagonistic blocking, whereas at higher dose levels, it exhibited autoantagonistic action. All the remaining compounds lack depolarizing properties. None of the compounds of Group 2 resulted in contraction of the frog rectus abdominis muscle, but when they were added to the bath before decamethonium, they revealed affinity for receptors, but no measurable intrinsic activity. (41 references)

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777 Barbato, L. M. & Abood, L. G. **Purification and properties of monoamineoxidase.** Biochimica et Biophysica Acta, 67:531-541, 1963.

In the purification of MAO from liver mitochondria, about 400 g of liver is homogenized in 3 volumes of 0.25 M sucrose. The thick suspension is diluted with doubly distilled water and Triton X-100 (to a concentration of 0.5%) and the pH adjusted to 7.0; the solution is centifuged 6 times at 800 to 100,000 X gravities. The supernatant fluid of the last centrifugation is adjusted to pH 8.5, calcium phosphate gel equal to 4 times the weight of protein added, and the suspension centrifuged at 5,000 X gravities. The last step is repeated, and the residue is discarded. All operations are performed at

0° to 5° C. The mitochondrial MAO obtained was found to be a sulfhydryl enzyme. Inhibition of this preparation by p-chloromercuribenzoate was apparent at 10^{-5} M and complete at 10^{-3} M. There is no indication of competitive inhibition of MAO by p-chloromercuribenzoate. With tyramine as a substrate, 10^{-3} M phenanthroline caused activation. Inhibition produced by phenathroline with kynuramine as substrate, although quite low, is neither noncompetitive nor competitive. Inhibition was competitive with phenylcyclopropylamine (kynuramine substrate), but, when the enzyme was incubated with the inhibitor before addition of the substrate, inhibition was both competitive and irreversible. The pH activity curve of MAO in the presence of iproniazid was similar to that of the enzyme alone, and had an optimum at pH 8.0. The inhibitory action of iproniazid was unaltered by gassing with nitrogen for 5 minutes, and it still produced 34% inhibition in an anaerobic system.

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778 Shulgin, A. T. **Psychotomimetic agents related to mescaline.** Experientia, 19:127-128, 1963.

Phenethylamine derivatives (C_2H_5 through C_7H_{15}) of nitrostyrenes, comprising higher homologs of dl-trimethoxyamphetamine, were synthesized. Toxicity and behavioral studies with mice could not distinguish between the first three members of this series. Mild, agitated behavior was produced by doses of 80 mg per kg of all the test compounds, with complete recovery occurring within 8 hours. The LD_{50} was between 200 and 300 mg per kg, i.p., for all compounds. Trimethoxyamphetamine was more than twice as potent as mescaline in human subjects. At oral levels above 2.5 mg per kg, α-ethyl mescaline produced neither central activity nor psychic disturbance. This indicates a psychotomimetic potency less than half that of trimethoxyamphetamine, and suggests that three carbon atoms represent the optimum chain length.

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779 Mannarino, Emanuele, Kirshner, Norman, & Nashold, Blaine S., Jr. **The metabolism of [C^{14}] noradrenaline by cat brain in vivo.** Journal of Neurochemistry, 10:373-379, 1963.

Mature cats were lightly anesthetized with sodium amytal. With the aid of a sterotoxic instrument, injections of 35μg of [C^{14}]noradrenaline containing 2μC of radioactivity in a constant volume of 0.1 ml of physiological saline were made into the left lateral ventricle. One ml blood samples were collected from the jugular vein and, sometimes, from the femoral vein at 5-minute intervals during the first hour and at 30-minute intervals for the next 2 hours. Urine samples were collected via catheter at 1-hour intervals. After 3 hours, the cats were killed with an intracardiac injection of nembutal, and the brain was removed and separated into cerebrum and cerebellum. Animals pretreated with iproniazid received three 50 mg doses i.p. at 24, 15, and 3 hours before noradrenaline injection. The studies indicate that catechol-O-methyltransferase plays the major role in the inactivation of adrenaline and noradrenaline injected into the lateral ventricle of the cat. The [C^{14}] noradrenaline was catabolized mainly to normetadrenaline and 3-methoxy-4-hydroxyphenylglycol in the cerebrum and cerebellum. The principal catabolites in the urine were normetadrenaline and a conjugate of 3-methoxy-4-hydroxy-phenylglycol. Aproniazid had little effect on the metabolism of noradrenaline in the brain, but appeared to inhibit oxidative deamination of the amines that entered the systemic circulation.

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780 Yung, D. K. & Pernarowski, M. **Identification and differentiation of some phenothiazine-type tranquilizers.** Journal of Pharmaceutical Sciences, 52:365-370, 1963.

The following substituted phenothiazines were investigated: acepromazine HCl, chlorpromazine HCl, fluphenazine, levomepromazine maleate, meprazine acetate, perphenazine, prochlorperazine dimaleate, promazine HCl, thiopropazate dihydrochloride, thioridazine HCl, trifluoperazine dihydrochloride, triflupromazine HCl, and trimeprazine tartrate. A number of procedures are described that will aid the pharmaceutical analyst in rapid identification. Tests include color formation, melting points, and infrared spectra. The techniques were applied in analyzing 12 commercial preparations containing various substitute phenothiazines. One of the preparations, containing fluphenazine in concentrations equal to 0.25 mg per tablet, could not be identified by using the methods described herein because of the difficulties encountered in extracting this quantity of active

gredient from the tablet mass. No diffi-
lties were encountered with the rest of the
eparations.

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81 Koren, Z., Brzezinski, A., Pfeifer, Y., & Sulman, F. G. **Seretonin pro-
uction in spontaneous and Caesarean deliv-
y.** Journal of Obstetrics and Gynaecology
the British Commonwealth, 70(3):483-486,
963.

rine samples were analyzed from two groups
women (ages 18 to 38) who were in various
tages of labor. In one group of twenty-four
omen who delivered vaginally without anes-
hetic, three urine samples were taken: one
pon admission (if cervix was dilated 1 to 2
n and contractions were regular), one im-
ediately after expulsion of the fetus, and
ne 24 hours after delivery. The other group
f 11 women were delivered by elective
aesarian section and were given a general
nesthetic. Three urine samples were taken:
ne just before anesthesia, one just after
ne operation, and one 24 hours postopera-
ive. Values of 5HIAA varied between 1µg
nd 28µg per ml in both groups, regardless
f the mode of delivery. When calculated in
aily values or compared with similar tests
n normal patients and on 63 pregnant women
n all stages of pregnancy, no difference in
HIAA excretion was found in either group.
n pregnant women with an anamnesis of habit-
al abortion, very high peaks of 5HIAA were
bserved on days of mental or physical
tress. These peaks went as high as 43 mg
er day and reverted to normal values on the
ollowing days. The significance of high
rinary values of 5HIAA due to stress in de-
ivery is discussed, and the possible use of
his examination for measuring fear and men-
al stress of women in labor is advocated.

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82 Yamamoto, Yasuhisa, Iwado, Takaaki, Kitamura, Motoo, Uno, Kazumasa, & ugiu, Ryosuke. **Amino acids in the brain—— nalysis of amino acids in various areas of he cerebral cortex.** Folia Psychiatrica et eurologica Japonica, 17(3):299-305, 1963.

uantities of glutamic acid, glutamine, ABA, and other free amino acids were deter-
ined in the brain to help in the treatment f disorders of the CNS. The authors feel that these amino acids are material to the smooth functioning of the brain. Brains were obtained at autopsies performed 16, 10, and 6 hours after death on three patients who had had no disease of the brain. The patients had been right-handed; therefore, materials were taken from the frontal, motor, sensory, speech, and occipital areas of the left hemisphere in the shape of discs 3 cm in diameter. The amino acids were extracted by the ion-exchange method of Stein. Unknown amino acids were analyzed by the "improved system" of Moore. Acidic, neutral, and basic amino acids were analyzed and identified by ion exchange, using Dowex 1-X8 and Amberlite IR 120 resins. Results of the analysis of the three brains are tabulated. Glutamic acid and glutamine are both predominant in each area of the brain. Glutamine is more predominant in the motor and occipital areas. Glutamine either plays an important role in these areas, or else the interrelation between it and glutamic acid is very active. Phosphoethanolamine is in greatest quantity in the frontal and motor areas, and appears to be important in the metabolism of amino acids containing phosphorus in the anterior area. Cystathionine is in large quantity in the sensory, speech, and occipital areas, and appears to play a metabolic role in the metabolism of amino acids containing sulfur. GABA appears to be greatly affected by postmortal changes, and is important in the physiological and biochemical vital reactions of the brain. The authors emphasize the difficulty of substantiating suppositions and of drawing conclusions from them because of the subject matter.

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783 Brunjes, Shannon & Wybenga, Donald. **Differential fluorometry in catecholamine determination: A simplified method of calculation.** Clinical Chemistry, 9(5): 626-630, 1963.

To determine epinephrine and norephinephrine, measurements were made with two different sets of excitation and fluorescence wavelengths, chosen to maximize the difference between the relative readings of the two substances, while the absolute readings are kept relatively large. The concentration of each substance is then determined by solving two equations simultaneously. A simplified method for making these calculations is described.

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784 Huang, Chian Li, Sands, Freeman L., & Kurland, Albert A. **Urinary thorazine metabolites in psychotic patients.** Archives of General Psychiatry, 8:301–307, 1963.

An analytical study was made of daily urine excretion of unchanged chlorpromazine, chlorpromazine sulfoxides, hydroxychlorpromazine, and chlorpromazine glucuronides of seven chronic schizophrenic patients receiving chlorpromazine in doses of 300 to 1,200 mg daily. Up to 69% of the administered dose (average, 58%) was recovered from the metabolites. The chlorpromazine glucuronides were found to be the major urinary metabolites of chlorpromazine. Average 24-hour excretion of the four groups of metabolites in seven patients over a period of 30 weeks was: chlorpromazine glucuronides, 44.6%; hydroxychlorpromazine, 4.8%; chlorpromazine sulfoxides, 7.7%; and unchanged chlorpromazine, 1.1%. The procedure for separating the hydroxychlorpromazines and chlorpromazine glucuronides is described. There are some indications that the prolonged excretion of chlorpromazine glucuronides may be related to a slower rate of psychiatric relapse in these patients.

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785 Feldstein, Aaron, Wong, Keith Kam-Kim, & Freeman, Harry. **The metabolism of serotonin administered by the intramuscular and intravenous routes in normal subjects and chronic schizophrenic patients.** Journal of Psychiatric Research, 2:41–49, 1963.

Twelve chronic schizophrenic inpatients were selected for study. Their mean age was 48 years, mean body surface area 1.7 m^2, and mean hospital stay 14 years. They were denied drugs for at least 2 months. As controls, 12 nonpsychotic, healthy hospital workers were employed. Their mean age was 38 years, and mean body surface area 1.8 m^2. Both groups were composed of 6 men and 6 women. Each subject received one i.v. and one i.m. injection of 5 to 10 microcuries of serotonin-C^{14} creatinine sulfate. Urine samples were collected about 2, 8, and 24 hours after the injection. The major metabolite by either route of administration was 5HIAA. There was a marked delay in urinary recovery of total C^{14} and 5HIAA-C^{14} after i.m. injection of serotonin-C^{14}, which was maximal at 2 hours but clearly observable at 8 hours after injection. There were no statistically significant differences between the schizophrenic and the normal subjects in the recovery of total C^{14} or 5HIAA-C^{14}, by the i.m. or i.v. routes, calculated on the basis of total C^{14} in the urine. It was concluded that MAO and aldehyde dehydrogenase functioned normally in the schizophrenic population.

Worcester Foundation for Experimental Biology
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786 Henkin, R. I. & LaBrosse, E. H. **A method for enzymatic hydrolysis of conjugated epinephrine (E) and norepinephrine (NE) and studies of the specificity.** (Abstract) Federation Proceedings, 22:390, 1963.

Enzymatic hydrolysis of conjugated epinephrine and norepinephrine was performed to determine its specificity in the urine of normal volunteers and patients with pheochromocytomas and neuroblastomas. The hydrolysis, using purified sulfatase and glucuronidase, was done on the initial effluent of an alumina column. Recoveries of added tritium-labeled and unlabeled forms of these hormones and of epinephrine glucuronide were significantly higher than recoveries after acid hydrolysis. Extraction of the final acetic acid eluate with ethyl acetate removed much of the interfering fluorescent material found, especially in urine of patients with catecholamine-secreting tumors. The acetic acid eluates were assayed before and after paper chromatography on parallel chromatograms, one of which was sprayed for catechols. Areas corresponding to catechols were cut out and eluted. Epinephrine and norepinephrine in these eluates (as percent of initial assay) were 63% and 95% for the free hormones and 70% and 100% for the conjugated form, respectively. (Author abstract, edited)

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787 Mirkin, Bernard L., Giarman, Nicholas J., & Freedman, Daniel X. **Uptake of noradrenaline by subcellular particles in homogenates of rat brain.** Biochemical Pharmacology, 12:214–216, 1963.

Studies were done to determine whether subcellular particulate fractions from rat brain could concentrate and bind exogenous noradrenaline. Subcellular fractions were prepared at 4° C from freshly excised whole brains of decapitated male rats (200 g, Sprague-Dawley). After homogenation, then centrifugation, the cloudy supernate (25-ml aliquot) was decanted and incubated with

e priming amine (catecholamine) for 30 nutes at 37° C. The noradrenaline con- nt, estimated fluorometrically, was .7±9 mμg per g of whole brain (standard ror of the mean). Incubation of unprimed actions at 37° C for 30 minutes caused a rked decrease in the level of particulate- und noradrenaline, whereas the loss occur- ng at 4° C was minimal. The uptake of ex- enous catecholamine was determined by ad- ng noradrenaline (40 mμg per ml) to the cubation medium at zero time and estimat- g the noradrenaline content of the high- eed sediment after 30 minutes incubation. ximal uptake ranged from threefold to urfold above control levels, probably used by firm binding of the amine. Admin- tration of reserpine (5 mg per kg i.p.) to e rat 24 hours prior to the experimental riod diminished the uptake capacity of the bcellular fractions prepared from these imals, but it did not effect a complete ock. These data show that subcellular actions of rat brain possess a mechanism r concentrating exogenous noradrenaline milar to that shown for other neural ructures.

le University School of Medicine
w Haven, Connecticut

8 Lasslo, Andrew, Waller, Pauline D., & Epperson, Glenda J. **The synthesis of ylalkylaminopropionamide analogs of lyser- c acid diethylamide and their effect upon olated cholinesterase systems.** Journal of dicinal Chemistry, 6:26–28, 1963.

series of α-arylalkylaminopropionic acid ethylamides patterned after a component of e LSD molecule was synthesized, and their fect upon isolated human plasma pseudocho- nesterase systems was studied. Relation- ips between molecular structure and bio- emical response were also explored, and ta are included. The effect of a given mpound was calculated at four appropriate ncentrations, with at least two indepen- nt duplicate determinations for each con- ntration, and the molarity of the compound fecting 50% inhibition was determined aphically. The data further substantiate ndings previously reported by the authors:) the α-methylbenzyl derivatives are more tent inhibitors than the benzyl-substitu- d ones; (2) the benzyl derivatives effect aker inhibition than the phenethyl-substi- ted ones; and (3) neither of the enantio- rs of the (±)-α-methylphenethyl analog re- aled any pronounced specificity in either e α- or β-aminopropionamide series. Spe- fically, in the α-aminopropionamide series e phenethyl-substituted analog is more than 10 times stronger in its inhibitory effect than the benzyl-substituted one, and in the β-aminopropionamide series the corresponding phenethyl compound is less than three times as potent an inhibitor as the respective benzyl derivative. Work toward a comprehensive interpretation of the present and previous findings is in progress.

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789 Shanthaveerappa, T. R., Nandy, K., & Bourne, G. H. **Histochemical studies on the mechanism of action of the hallucinogens d-lysergic acid diethylamide tartrate (LSD-25) and d-2-bromo-lysergic acid tartrate (BOL-148) in rat brain.** Acta Neuropathologica, 3:29–39, 1963.

The mode of action of the psychomimetic drugs LSD-25 and d-2-bromolysergic acid tartrate (BOL-148) and their inhibition of different enzymes in various parts of the rat brain were investigated. Various previously published methods were used to study both the normal sites of localization of specific cholinesterase, nonspecific cholinesterase, and MAO, and the effects of the drugs on these enzymes. The brains of young adult albino rats were frozen and cut 10μ thick. Previously, both LSD-25 and BOL-148 were administered by i.p., i.v., or intracardiac injection in doses of 0.1 mg per kg, and the animals were killed within $\frac{1}{2}$ to 1 hour later. Time of sacrifice was decided by observed behavioral changes. As controls, the brains of untreated normal rats of the same age were studied. Also, untreated, normal, rat-brain sections were incubated with (0.1 mg per 10 ml of media) and without the drugs. Some sections were first placed in a normal saline-drug mixture before being incubated, and others were incubated without drug pretreatment. The normal localization of specific cholinesterases and MAO is inhibited by both LSD-25 and BOL-148. The degree of positive reaction for acetylcholinesterase and MAO is more intense in the basal ganglia and thalamus, and the inhibitory effect of the drugs is also profound in these regions. Possible mechanisms of these reactions are discussed, including the suggestion that the inhibition of MAO results in more accumulation of adrenaline, which is probably oxidized to adrenochrome, the latter acting as an hallucinogen in the body.

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790 Kanter, Saul L. **Elimination of interference due to urea in the determination of meprobamate with p-dimethylaminobenzaldehyde.** Clinica Chimica Acta, 8:2–4, 1963.

An extraction procedure for eliminating interference in drug determination is presented. One drop of glycerol-urease extract is added to 1-ml aliquots of water (reagent blank), serum, and meprobamate standards, which are then incubated at 50° C for 15 minutes. Tables are presented, illustrating the effectiveness of urease to reduce predrug levels to zero and, at the same time, eliminate the equivalent interference in postdrug samples. Urease does not affect the drug as it is being extracted from either water or serum.

Veterans Administration Hospital
Palo Alto, California

791 Khazan, N., Adir, J., Pfeifer, Y., & Sulman, F. G. **Mechanism of the antidiuretic action of reserpine.** Proceedings of the Society for Experimental Biology and Medicine, 109:32–35, 1962.

A study was made to determine whether release of antidiuretic hormone or serotonin depletion predominates in effecting reserpine antidiuresis. Twelve male dogs weighing 6 to 10 kg were divided into four equal groups, anesthetized i.p. with 30 mg per kg of sodium pentobarbital, hydrated with 10 ml per kg of water through a stomach tube, and then tracheotomized and cannulized. Following a laparotomy, the ureters were catheterized. Each group of animals received i.v. either 0.5 mg per kg of reserpine, 2 mg per kg of serotonin, 2 units per kg of antidiuretic hormone, or a reserpine solvent. Immediately thereafter, a second water load of 20 ml per kg of water was given. One hour after injection, urine was collected for 3 hours. At hourly intervals, the urine was measured and analyzed for Na^+, K^+, Cl^-, and 5HIAA. Since pentobarbital sodium has an antidiuretic effect, a parallel experiment was run in unanesthetized adult male rats. These experiments showed that the barbiturate does not interfere with the results obtained with regard to antidiuresis or to the patterns of Na^+, K^+, Cl^-, and 5 5HIAA urinary excretion. After administration of either reserpine or serotonin in dogs, the urinary excretion of electrolytes, chlorides, and 5HIAA was found to be similar in pattern: lower Na^+ and Cl^- and higher K^+ and 5HIAA. Antidiuretic hormone administration, however, resulted in a different pattern: higher Na^+ and Cl^- and lower K^+ and 5HIAA. This suggests that the antidiuretic action of reserpine is due to release of serotonin depleted from body stores, and not to release of antidiuretic hormone.

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See also: 578, 626, 628, 637, 678, 682

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792 LaVerne, Albert A., ed. **Compendium of neuropsychopharmacology.** Journal of Neuropsychiatry, 4(6):417-435, 1963.

Part II, Neuropharmacology, Section A, Anti-Epileptics, of the Compendium of Neuropsychopharmacology is presented in tabular form. The following information is given for each drug: generic name, trade name, and manufacturer; type and action; indications for use; effectiveness and toxicity; side effects; contraindications and caution; recommended dosage; and references. All terms are defined. The following drugs are included: phenobarbital, amobarbital sodium, methobarbital, metharbital, primidone, diphenylhydantoin sodium, methylphenylethylhydantoin ethotoin, phethenylate sodium, trimethadione, paramethadione, phensuximide, methsuximide, ethosuximide, phenacemide, aminogluthethimide, acetazolimide, ethoxyzolamide, sodium and potassium bromides, meprobamate, methamphetamine, amphetamine, and quinacrin hydrochloride. The drug ratings and other information listed are subject to revision as the future literature indicates.

(No address)

793 Brodie, David A., Hanson, Harley M., Sines, J. O., & Ader, Robert. **Current research on gastric ulcers.** Journal of Neuropsychiatry, 4(6):388-408, 1963.

The problem of experimental production of gastric ulcers is reviewed, with special emphasis on the restraint technique. A review of the literature gives major emphasis to the French research and the work of some American investigators. Details of the genetic susceptibility to stress-induced gastric lesions, the relationship between blood pepsinogen and restraint-induced ulcers, and some of the pertinent problems still under investigation are discussed.

Merck Institute for Therapeutic Research
West Point, Pennsylvania

794 Hordern, Anthony. **Psychiatry: Past and present. The "organic" approach.** Journal of Neuropsychiatry, 4(6):356-365, 1963.

A brief historical review of the organic approach to psychiatry is followed by a discussion of the work of three "organicists," Wilhelm Griesinger, Henry Maudsley, and Emil Kraepelin. Comments on "the organic approach today" are included.

Mental Health Research Institute
Victoria, Australia

795 Carr, D. J. & Crampton, R. F. **Ethclorvynol.** (Letter) British Medical Journal, 1(5325):262, 1963.

Comments on a previous article on ethchlorvynol, in which the adult hypnotic dose is stated to be 250 mg, are given. It is suggested that the adult hypnotic dose of ethchlorvynol ranges from 500 mg to 1 g, and that the liver is involved in the metabolism of the drug. Although an intake of 49.5 g of ethchlorvynol has proved fatal, smaller amounts have had the same effect and persons who have taken amounts larger than 25 g have survived. The point that ethchlorvynol may exhibit an exaggerated effect if taken with, or shortly after, alcohol is again made.

Abbott Laboratories, Ltd.
Kent, England

796 Blenkner, Margaret. **Control groups and the "placebo effect" in evaluative research.** Psychological Abstracts, 959:52-58, 1963.

Two control-group designs, both developed for research in aging, are discussed. The Jahn--Blenkner design is both sample survey and experimental design, and is used to study the utilization and effectiveness of casework and public-health nursing services for the aging. The Kogan—Posman design is closer to the usual control-group study and does not contain survey aspects; it is used to determine the effectiveness of public-health nursing in the rehabilitation of geriatric patients. A critique of designs and a discussion of controlled clinical trial and of placebo effects are also included.

Institute of Welfare Research
New York, New York

797 Lucas, George H. W. & Fabierkiewicz, C. Useful tests to identify phenothiazine tranquillizers. Journal of Forensic Sciences, 8(3):462-476, 1963.

Colorimetric tests were developed for determining phenothiazine and its derivatives. A color reaction involving bromine and concentrated sulphuric acid produces an immediate violet color that is stable for days, has an absorption peak at 580 mμ, and is suitable for all phenothiazines tried with the exception of trifluo-derivatives (red color, absorption peak at 540 mμ). Phenothiazine itself and its 5-oxide give the violet color only after a considerable elapse of time and much mixing of the reagents. A spot plate test is used with solid material. A drop or two of saturated bromine water is stirred into the solid. When the concentrated acid is added, the violet color appears in 15 to 60 seconds. Both insufficient or excess bromine must be avoided. In the test tube test for phenothiazines in solutions, 1 to 2 drops of bromine water are added to 1 to 2 ml test solution. The tube is shaken vigorously for 1 minute, and excess bromine is removed by aerating with compressed air blown through a capillary tube. Concentrated acid is added in drops (volume equal to that of original test solution) during constant vigorous agitation. Maximum color develops in 4 to 5 minutes. Intermediate color reactions are described, and spectrophotometric data for many phenothiazine derivatives are given. As little as 1 γ of a phenothiazine-type material may be determined by these methods.

University of Toronto
Toronto, Canada

798 DeGraff, Arthur C., & Lyon, Alan F. Mebutamate. Antihypertensive or tranquilizer? American Heart Journal, 65:569, 1963.

Mebutamate has been described as a mild antihypertensive agent with central action. From the available evidence, it appears that mebutamate is primarily a sedative or tranquilizer, and that any effect it may have on hypertension is due to sedation and not to any specific action directed primarily to the reduction in blool pressure alone.

850 Park Avenue
New York, New York

799 Thuillier, Jean. La neuro-psychopharmacologie perspectives expérimentales et intérêt clinique. (Neuropsychopharmacology experimental prospects and clinical value.) Le Concours Medical, 85(1):47-57, 1963.

Psychopharmacology was born in 1952 to 1954 with the discovery of the remarkable effects of chlorpromazine and reserpine on mental pathology. This suggested that certain mental illness can be caused by disturbance of the biochemical homeostasis of metabolism. The biochemical origin of certain psychoses was indirectly verified by the production of artificial psychic disturbances similar to certain pathological mental states by hallucinogenic drugs, such as mescaline, lysergamide, and psilocybin. This, in turn, suggests that improving knowledge of the biochemical mechanisms responsible for drug-produced psychoses would improve knowledge of spontaneous psychoses. There are three distinct areas of neuropsychopharmacology at the present time: (1) psychopharmacology of hallucinogenic drugs; (2) psychopharmacology of psychiatric drugs, which may be called therapeutic psychopharmacology, dealing with research on new psychotropic drugs and including animal tests; and (3) biochemical psychopharmacology, the ideal goal of which is research on the biochemical causes of certain psychoses. At present, this area is limited to the study of the metabolism of psychotropic drugs and the effects of psychotropic drugs on the metabolism of amines, enzymes, and neurohormones. The neuropsychopharmacology of the future will be biochemical, studying homeostatic deviations in mental patients, permitting interpretation of the biochemical mechanism of organic psychoses, and eventually resulting in cure of organic mental disturbances by biochemical therapeutics.

(No address)

800 Forrest, Fred M. & Forrest, Irene S. Urine testing for phenothiazine and related drugs. Its significance for achieving and maintaining rehabilitation of chronic mental patients. American Archives of Rehabilitation Therapy, 10(1):1-8, 1963.

The use of urine testing for the detection of phenothiazine and related drugs in the rehabilitation of chronic mental patients is examined. Experience has shown that the FPN test for phenothiazine is reliable in detecting the intake of as little as 20 mg per day of any phenothiazine compound, administered chronically. With lesser doses, especially in a single drug administration, testing should be performed 1-½ to 3 hours after drug intake (the time of optimum drug excretion). In the era before drug therapy, the recovery rate in a group of over 1.000 severely ill,

chronic mental patients (severe psychotic manifestations) was 2% to 4%. After intensive treatment for 9 years with phenothiazine drugs, over 50% of the same group of patients were discharged from the hospital. It was found that drug doses of up to 400 mg of chlorpromazine per day or equivalent doses of trifluprom azine, and subsequently, thioridazine, even when given for 6 months or longer, will in many cases be inadequate for changing psychotic to nonpsychotic behavior in long-term patients. Maximum doses (up to several thousand mg) frequently must be given uninterruptedly for many months (in some cases up to 18 months) to effect successful rehabilitation. Monthly urine tests on discharged patients were matched against hospital records to ascertain if the patient's medication intake was being continued. A negative FPN test means that a patient has no urinary phenothiazine level and has ingested no drugs, or less than the required 20 mg, on the day of the test.

Veterans Administration Hospital
Palo Alto, California

801 Vikhlyayev, Yu. I., & Lyubimov, B. I. **Psychopharmacologic agents of the depressant type.** Vestnik Akademii Meditsinskikh Nauk SSSR, 16(10):78-82, 1961.

A review is given of psychopharmacological agents that act as depressants. The classification was based on the following characteristics: (1) ability to depress spontaneous motor activity of experimental animals; (2) ability to potentiate the action of anesthetics, hypnotics, and, in part, analgesics; (3) depression of polysynaptic reflexes of the spinal cord; (4) depression of sympathetic nervous system; (5) depression of the parasympathetic nervous system; (6) lack of effect on the autonomic nervous system; (7) influence on the electroencephalographic picture of "arousal reactions"---partial or complete elimination of the arousal reaction, or lack of effect on this reaction; and (8) types of side effects produced. Drugs representative of each category are listed. An extensive discussion of the phenothiazines is given, with special emphasis on thorazine. Changes in pharmacological activity resulting from modifications of the thorazine molecule are listed.

Joint Publications Research Service
Ohio Drive and Independence Ave., SW.
Washington 25, D.C.

802 Hypnotics---1. Barbiturates. (Editorial) British Medical Journal, 1(5322): 39-40, 1963.

Barbiturate hypnotics are considered in the first of a series of articles intended to survey "today's drugs." Official name, proprietary name, substitution groups, and dosage are given for each of eight barbiturates; further information is furnished concerning their chemistry, pharmacology, classification, therapy, contraindications, and side effects.

(No address)

803 van Rossum, J. M. **The relation between chemical structure and biological activity. Discussion of possibilities, pitfalls and limitations.** Journal of Pharmacy and Pharmacology, 15:285-316, 1963.

The author discusses the following: qualitative action and quantitative activity of drugs; drug moieties necessary for affinity with receptors; basic steps in drug action (attainment of the biophase environment by drug molecules, drug-receptor interaction, and relationship between drug stimulus and ultimate effect); intrinsic activity as a measure of agonistic potency; dose-response measurement of affinity and intrinsic activity; agonists, competitive and noncompetitive antagonists (size of molecule, change from agonist to antagonist); interpretation of in vivo experiments; tissue and species differences for drug affinity and intrinsic activity; optimal affinity of drug molecular conformation and flexibility of the receptor (enantiomorphs and racemates); key position of molecular asymmetric center in respect to affinity or intrinsic activity; parasympathomimetic (muscarinic) and antiacetylcholine drugs and their receptor sites (ganglia, skeletal--myoneural junction); histaminomimetic, histaminolytic, and sympathomimetic drugs; and psychomotor stimulants. (75 references)

Catholic University of Nijmegen
The Netherlands

804 Bowman, Karl M. & Engle, Bernice. **Geriatrics.** American Journal of Psychiatry, 119:652-654, 1963.

Many symptoms of the aging process are reported, including the loss of neurons in the brain and the lessened brain weight, which

greatly impair mental ability. Some authors suggest that aging can be controlled by altering biochemical and biophysical processes. Shock's 10 facts about aging are listed. A Russian study states that rural living promotes long life, but a large-scale study of aged Kentuckians did not prove this theory. Many comparative studies have found that health status, and not age per se, determines the degree of relationship between EEG and intelligence. From a sampling of reports on various psychopharmacological therapies, phenothiazine drugs in high dosages benefited aged paranoics; nialamide therapy benefited aged depressives; ethyltryptamine was an effective energizer in aged patients with parkinsonism and reactive depression; and EST proved effective in depressed schizophrenics. Morale is said to be an important factor in the aged. Attempts to increase self-care and activity in aged patients bring improvement. In a five-state study, positive factors for good adjustment were marriage, home ownership, high-school education or better, and participation in community activities. Aging, in one study, is defined as decreased interaction between the geriatric and his social milieu.

University of California
San Francisco, California

805 Sandifer, Myron G., Jr. **The "double blind".** (Letter: comment on letter by Joseph A. Barsa.) Barsa, Joseph A. Reply to the foregoing. (Letter) American Journal of Psychiatry, 120:508–509, 1963.

A comment by Dr. M. G. Sandifer* on a paper by Dr. J. A. Barsa** ("The Fallacy of the 'Double-Blind'"), and Dr. Barsa's reply to the comment are given. Dr. Sandifer takes issue with the three criticisms of double-blind studies given by Dr. Barsa, namely that most double-blind studies are too brief for proper evaluation of the drugs; dosage requirements are not individualized; and the side effects of a drug often betray the drug, and the study is no longer "blind." In his reply, Dr. Barsa refutes Dr. Sandifer's arguments against the criticisms and repeats that, although he agrees with the purpose of the double-blind study, i.e., objective validity, it is merely one method of control that has limited usefulness in psychiatry.

*North Carolina Hospitals
Raleigh, North Carolina

**Rockland State Hospital
Orangeburg, New York

806 Eysenck, H. J., ed. **Experiments with drugs.** New York, MacMillan, 1963. 421 p.

This book contains the following chapters: (1) Personality and Drug Effects; (2) The Suppression of the Primary Visual Stimulus; (3) "Visual Masking" and the Effect of Stimulant and Depressant Drugs; (4) The Effects of Stimulant and Depressant Drugs on Auditory Cross-Masking; (Appendix: Interrelations between two Measures of Perceptual Inhibition); (5) Excitation-inhibition and the Theory of Neurosis: A Study of the Sedation Threshold; (6) A new Method for the Determination of Individual Differences in Susceptibility to a Depressant Drug; (7) The Effects of Meprobamate on the Visual After-Image; (8) The Effects of Meprobamate on the Spiral After-Effect; (9) The Effects of Stimulant and Depressant Drugs upon Visual Figural After-Effects; (10) The Effects of Meprobamate on Apparent Movement; (11) Depressant-Stimulant Drugs, Inhibition and the Visual Constancies; (12) Brain-damage and Depressant Drugs: an Experimental Study of Interaction; (13) Some Effects of Carisaprodol on Pain Reactivity; (14) Ethyl Alcohol and the Effects of Stress; and (15) The Influence of Stimulant and Depressant Drugs on the Central Nervous System.

(No address)

807 Mills, Enid C. **The family doctor and the mental health services.** Medical World, 98:105–110, 1963.

Evaluation of the consequences of continuing or discontinuing any particular drug requires close cooperation between the general practitioner and the psychiatrist or the mental health service. Psychiatrists often prescribe new or special drugs that may not be familiar to the general practitioner. These drugs may have unpleasant or serious side effects. The family doctor tends to underestimate the psychiatric consequences of stopping or changing such drugs, and the psychiatrist tends to underestimate the physical discomfort to the patient. The family doctor may yield to a patient's requests to discontinue a drug, thus resulting in serious illness that necessitates rehospitalization.

(No address)

808 Frommer, Eva. **Physical treatments in psychiatric nursing——3. The schizophrenias.** Nursing Times, 59:261–262, 1963.

The first choice of tranquilizer in most schizophrenic cases is either chlorpromazine or perphenazine. With high dosage, side effects appear rapidly---stiffness of the muscles, pains in the legs, difficulty in focusing, and excessive salivation. Phenothiazine may produce a considerable drop in blood pressure, and a large difference between blood pressure taken while sitting and on standing up may require revision of treatment. Drowsiness indicates that dosage should be reduced, and it may also be a sign of clinical improvement. Paranoiac schizophrenics often respond well to trifluoperazine, which produces side effects in 24 hours, even in small doses. This drug should be given together with an antiparkinsonian drug from the outset. Monoamine oxidase inhibitors will precipitate latent schizophrenia. Drugs may be tapered off after the patient is free of symptoms for 6 months to a year. In case of relapse, treatment must be maintained for years under outpatient supervision.

(No address)

809 Baruk, Henri M. **La psychopharmacologie expérimentale chez les animaux et la prévention des accidents des nouveaux médicaments psychotropes. (Experimental psychopharmacology of animals and prevention of accidents due to new psychotropic agents.)** Académie Nationale de Médecine, 147:43-46, 1963.

To prevent human accidents when using drugs, animals that are given drugs should be kept for months and, sometimes for years. Some animals should be administered drugs over prolonged periods in order to observe the effect of dose accumulation. This prolonged action must be followed in certain cases by anatomic and histologic studies of the brain. Each drug should be applied, at least, to fish, amphibians, reptiles, birds, and mammals, including in particular mice and monkeys. Determination of the effects of drugs on the cerebral circulation in monkeys is especially useful. Rats and chickens are the least desirable for psychopharmacological investigation because of their susceptibility to animal hypnosis, which often distorts results.

(No address)

810 Barsa, Joseph A. **The fallacy of the "double blind".** American Journal of Psychiatry, 119:1174-1175, 1963.

The validity of the double-blind study, where neither patient nor investigator is aware of the nature of the medication, to investigate psychotropic drugs is refuted. A drug was given at a predetermined dose to a random sample of patients, and a placebo that had the same appearance as the drug was given in the same dosage to a comparable sampling of patients. At the end of a predetermined period, the patients' degree of improvement was evaluated. This testing was often followed by a crossover, and the results were again evaluated. Some false premises can be noted. For example, the study disregards the individual dosage needs of the patients, as well as the fact that a tranquilizer has two separate and distinct actions, one of which may not be detected until completion of the study and, therefore, gives an invalid picture of the effectiveness of a drug. In order to include varying dosage needs, some studies were designed where a fixed dose was given for 1 to 3 months; thereafter, the physician could change the dosage to comply with his clinical judgement, although which medication was the placebo and which was the active drug was not known. The increased dosage eventually produced side effects that betrayed the nature of the drug being tested. The double-blind study adds to the confusion in a drug investigation by its many half-truths and unwarranted conclusions.

Rockland State Hospital
Orangeburg, New York

811 Zakusov, V. V. **O nekotorykh antagonistakh serotonina. (Certain serotonin antagonists.)** Farmakologiya i Toksikologiya, 26(2):131-138, 1963.

The effect of serotonin on myocardium and the possible use of serotonin antagonists in circulatory disturbances are discussed. Nine types of serotonin antagonists are mentioned: alkaloids of ergot and their derivatives, indole compounds, antihistaminics, anesthetics, analgesics of the morphine group, phenothiazines, cholinolytics, sympathicomimetic amines, and adrenolytics.

Institute of Pharmacology and Chemotherapy
U.S.S.R.

812 Wang, Richard I. H. **Control of pain.** American Journal of Medical Sciences, 246(5):590-609, 1963.

The potentialities and limitations of existing methods advocated for the control of pain are reviewed. The nature, types, methods of evaluation, and neurophysiological pathways of pain are briefly presented, and principles for the management of acute and chronic pain are outlined. Characteristics and uses of narcotic analgesics, narcotic antagonists, and nonnarcotic analgesics are discussed. (105 references)

Roswell Park Memorial Institute
Buffalo, New York

813 Aird, Robert B. & Becker, Ronald A. **The blood-brain barrier in clinical disease: A review.** Journal of Nervous and Mental Disease, 136(6):517-526, 1963.

Studies of the blood-brain barrier (BBB) are evaluated and reviewed under the following topical headings: BBB Concepts, The Endothelial Component of the BBB, BBB Studies in Clinical Conditions, and Conclusions. (64 references)

University of California School of Medicine
San Francisco, California

814 U.S. Department of Commerce. **Neuroleptic syndrome.** Nadzharov, R. In: Bol'shaya Meditsinskaya Entsiklopediya, Vol. 29, Moscow, 1963, p. 605-608. (Joint Publications Research Service Report No. 22438; Office of Technical Services Report No. 64-21109.) Washington, D.C., Office of Technical Services, 1963. 4 p.

The reversible extrapyramidal disorders and psyche modifications that develop as side effects of neuroleptic drug therapy are discussed. The extrapyramidal disorders most frequently encountered are pseudoparkinsonism, hyperkinesia, and akathisia. Psychic changes include asthenia, indifference, delayed reaction to outer stimuli, neutrality of emotions and affections, diminished initiative and interests, and depression. The pharmacological features of the neuroleptic drugs influence the clinical characteristics of the neuroleptic syndrome. Reserpine and the phenothiazines, aminazine, propazine, and acetazine, can cause nonacute modifications of mental activity during the early part of treatment; with prolonged treatment, pseudoparkinsonism, akathisia, and depression may develop. With piperazine derivatives of phenothiazine (majentil, prochlorazine, etaperazine, and trilaphone) and butyrophenone derivatives (haloperidol and triperidol), the frequency of extrapyramidal disturbances is much greater; the hyperkinetic syndrome is also often noted. Prophylactic and therapeutic drugs to counter the neuroleptic syndrome are discussed, and dosages are recommended.

Joint Publications Research Service
Ohio Drive and Independence Ave., SW.
Washington 25, D.C.

815 Laverne, Albert A., ed. **Compendium of neuropsychopharmacology.** Journal of Neuropsychiatry, 4(2):127-133, 1962.

Section F, "Preparations Used in Treatment of Alcoholism," of the psychopharmacology portion of the compendium is presented in tabular form. For each compound, the following information is given: generic name, trade name, manufacturer, type and action, indications for use, effectiveness, toxicity, side effects, contraindications and cautions, recommended dosage, and references. All terms are defined. The charts will be revised as the future literature indicates. Some of the drugs used as adjuncts in the therapy of acute and chronic alcoholism are reviewed in other sections of the compendium.

(No address)

816 U.S. Department of Commerce. **Sedatives.** Mashkovskiy, M. In: Bol'shaya Meditsinskaya Entsiklopedya, Vol. 29, Moscow, 1963, p. 601-605. (Joint Publications Research Service Report No. 22438; Office of Technical Services Report No. 64-21109.) Washington, D.C., Office of Technical Services, 1963. 6 p.

A general review is given of sedative drugs. The term "sedative drug" is defined, and the various modes of action of sedative drugs are discussed briefly. Naturally occurring sedatives of plant origin, such as those derived from garden valerian, motherwort, and rauwolfia, are listed. The following synthetic preparations are described according to chemical structure: bromides, alcohols (monoatomic, cyclic, and multiatomic), urethans, ureides, and derivatives of barbituric acid. Certain phenothiazines, such as propazine and aminazine, and some antihistamine drugs are also described as having sedative properties. Combinations of drugs, which have shown sedative action, are listed and proportions are given.

U.S. Department of Commerce
Ohio Drive and Independence Avenue, SW.
Washington, D.C.

817 LaVerne, Albert A., ed. **Compendium of neuropsychopharmacology.** Journal of Neuropsychiatry, 4:280-284, 1963.

Part two (thiobarbiturates) of Section III (sedatives and hypnotics) of the compendium of neuropsychopharmacology is presented in tabular form. The following data are given for each drug: generic name, trade name, manufacturer, type and use, indications for use, effectiveness, toxicity, side effects, contraindications and cautions, recommended dosage, and references. The charts were compiled from current references reviewed by the editor, and will be revised as the future literature indicates. The topical headings used in the chart are defined.

(No address)

CLINICAL STUDIES

818 Gelfand, Sidney, Ullmann, Leonard P., & Krasner, Leonard. **The placebo response: An experimental approach.** Journal of Nervous and Mental Disease, 136(4):379-387, 1963.

Laboratory procedures were developed that allowed systematic investigation of the placebo situation with nonpathological subjects and identification of some of the personality correlates of placebo responsivity. Experimental subjects (47 nursing students) were tested for perception and tolerance of pain experimentally induced by an ultrasonic unit. As a second step, they were administered a placebo pill that was described as a new and powerful pain reliever, and were tested again. Fifteen controls participated in the same procedure but without the placebo. Correlations between response measures of the experimental group and California Psychological Inventory (CPI) scales were computed. Significant placebo responsivity was demonstrated by the finding that the experimental group had higher change scores than the control group for all three response measures (pain perception, pain tolerance, and total time). Low, but significant, correlations were obtained between experimental group pretrial pain-tolerance scores and the CPI scales. None of the partial correlations between CPI scales (dominance, social presence, and self-acceptance) and placebo responsivity measures were significant. The pain-perception and pain-tolerance placebo responsivity variables were differentially related to the Capacity for Status and Sociability CPI scales.

Veterans Administration Hospital
Palo Alto, California

819 Zapletálek, M. & Komenda, S. **Vliv lévomépromazinu na kalium, kalcium a fosfor u depresívních stavu. (The effect of levomepromazine on potassium, calcium and phosphorus in depressive states.)** Activitas Nervosa Superior, 5:182-183, 1963.

The effects of levomepromazine on K, Ca, and P ion levels in the blood were studied in 21 patients, 6 males and 15 females, 20 to 57 years old (average age, 37). The diagnoses were endogenous depression (11 patients), depressive schizophrenia (4), involutional depression (1), and depressive phase of cyclothymia (5). The blood levels were determined by flame photometry, using samples taken under basal conditions and samples taken on the following day, 2 hours after administration (route not indicated) of 50 mg levomepromazine. The values obtained were compared with the potassium--calcium quotient (K/Ca-Q) norm of Jesserer. The results showed that levomepromazine produced a sympathicotonic shift in vegetative tonus, as indicated by a drop in the values for K, Ca, and P ions, and by a decrease in the K/Ca-Q. This was confirmed by a paired t-test. The change in K/Ca-Q values was found to be independent of the age of the subjects. The authors confirmed clinical knowledge of the pronounced parasympathicolytic side effects of levomepromazine through their findings of depression of the central nervous system, and through the orthostatic condition of the vegetative nervous system, including tachycardia and dryness of the mouth.

PU, Olomouc
Czechoslovakia

820 Buffaloe, W. J., & Sandifer, M. G., Jr. **A study of combined therapy with stelazine and "parnate" (SKF 385) in chronic anergic schizophrenics.** American Journal of Psychiatry, 117:1030-1031, 1961.

Twenty male schizophrenics with an average age of 48 years and an average hospitalization of 22 years participated in this study. Primary manifestations of psychopathology were disinterest and inactivity. Most of the patients had been on a phenothiazine derivative prior to the study. All 20 patients were placed on trifluoperazine for 5 weeks, and weekly hospital adjustment ratings were made. After the fifth week, ratings were averaged, and the patients were divided into 2 groups of 10 each, using paired comparisons to distribute observed psychopathology equally. Group A received both trifluoperazine and tranylcypromine for 5 weeks, while Group B continued on trifluoperazine alone. Dosage of trifluoperazine averaged 20 mg daily.

Screening for possible toxic effects produced essentially negative results. Therapeutic effects were judged by an abbreviated form of the Hospital Adjustment Scale. The average for weeks 2 through 5 and weeks 7 through 10 was used for determining results. Differences in therapeutic benefits between the two groups were not significant.

Dorthea Dix Hospital
Raleigh, North Carolina

821 Sletten, Ivan W., Fusaro, Ramon M., & Runge, Walter J. **A new topical spray agent to protect patients on chlorpromazine from sunlight.** American Journal of Psychiatry, 119:991-992, 1963.

A new method, utilizing an aerosol mixture, of protecting patients on chlorpromazine from sunburn is described. The topical mixture consists of 0.035 percent lawsone and 3 percent dihyroxyacetone in a 50 percent isopropanol—water solution and produces a protective filter. Forty patients who had shown a masked sunburn reaction while on chlorpromazine were sprayed with the aerosol mixture on all exposed parts three times a day for 2 days, every other day for 2 months, then every 4 days for 1 month, and every 5 days for the last month. All patients were protected if they were adequately sprayed; some emotionally disturbed patients were difficult to spray. Each spraying required only a few seconds of staff time.

Hastings State Hospital
Hastings, Minnesota

822 Damrau, Frederic, Liddy, Emma, & Damrau, Adeline Maneery. **Value of stout as a sedative and relaxing soporific.** Journal of the American Geriatrics Society, 11(3): 238-241, 1963.

Fifty healthy patients of both sexes (average age of 51.8 years) who had trouble sleeping participated in a study of the sedative action of stout. The test consisted of drinking one bottle (11.39 fluid ounces) of stout before retiring, and reporting on drowsiness, quality of sleep, and nocturia. Three tests were performed on each subject, making a total of 150 tests. Sleep was improved in 114 tests. Drowsiness occurred in 82 tests, and noctura occurred in 8 tests. In a subgroup of 12 subjects who were users of sleeping pills, sleep was sounder in 21 (of 36 total) tests.

2 Tudor City Place
New York 17, New York

823 Shepard, H. L. **Treatment of edematous states and hypertension with bendroflumethiazide (naturetin).** Journal of the American Geriatrics Society, 11(4):363-368, 1963.

Twelve men (45 to 90 years old) and 16 women (35 to 75 years old), suffering from edema associated with heart disease, edema from other causes, hypertension, or hypertensive heart disease, were treated with bendroflumethazide alone or in combination with a potassium supplement. The dosage of bendroflumethazide varied from 5 to 15 mg daily, but in 19 patients, the lowest dose was continued for the duration of treatment. Each of the drugs was given initially to 14 patients, with transfers being made from one drug to another according to individual reactions. Fourteen patients received adjunctive medication concurrently (including digitalis, pentaerythritoltetranitrate, reserpine, and diuretics). In eight cases, bendroflumethazide was substituted for previous medication. The duration of treatment varied from 2 weeks to 9 months. Results were good in 14, fair in 9, and poor in 5 patients. In patients having various types of heart disease associated with fluid retention, subsidence of edema was rated good or fair in 14 and poor in 1. Three patients with other edematous conditions responded well or moderately well, and one responded poorly. Blood pressure was considerably or moderately lowered in three hypertensive patients; one responded poorly. The three patients with hypertensive heart disease all responded at least moderately well. No serious side effects or intolerance to bendroflumethazide developed. Symptoms of hypokalemia appeared in some patients (possibly due to digitalis intoxication), but these disappeared as soon as potassium was prescribed.

Medical Arts Clinic
Lubbock, Texas

824 Vinař, O., Grof, S., Váňa, J., & Matoušek, M. **Vztah mezi terapeutickým efektem a extrapyramidovými příznaky vyvolanými thioproperazinem. (Relation between the therapeutic effect and extrapyramidal symptoms during thioproperazine therapy.)** Activitas Nervosa Superior, 5:201-203,1963.

A statistical study was done of the condition of patients treated with thioproperazine in all the psychiatric establishments with inpatient facilities in Czechoslovakia to investigate the correlation between the frequency and strength of extrapyramidal symptoms. Therapeutic effects were evaluated on the basis of eight selected items of the FKP

scale, which may be considered as target symptoms, and on the basis of social adaptation of the patients. Frequency and intensity of extrapyramidal symptoms were judged according to five items of the VP scale: B (tremor), C (muscular rigidity), D (oral dyskinesia), E (akathisia) and O_2 (facies oleosa). Although the therapeutic results were significant in the patients surveyed, the therapeutic methods used prevented any statistical generalization. The 53 patients (12 males and 41 females) had an average age of 36.7 years (range 18 to 58), average duration of illness of 7.4 years (range 2 to 18); their diagnoses were as follows: schizophrenia (47), paranoia (2), obsessive neurosis (1), atypical mania (2), and melancholia (1). Patients discharged or permitted greater freedom as a result of treatment included 38 schizophrenics, 1 paranoic, and 2 with atypical mania. No change or aggravation was noted in the remainder. The statistical results did not indicate a correlation between the frequency and intensity of extrapyramidal symptoms: the Weichelt coefficient of correlation was -0.11.

Psychiatric Research Institute
Prague, Czechoslovakia

825 Šedivec, Vl. & Dvořáková, M. **EEG nálezy v průběhu léčení některými novějšími psychofarmaky. (EEG findings during therapy with some new psychotropic drugs.)** Activitas Nervosa Superior, 5:205, 1963.

The EEG tracings were studied of 26 patients treated with chlorprothixene, 19 patients treated with Theralen, and 12 patients treated with Prothiadene. The 57 patients included 15 males and 42 females, aged 18 to 67 years. The diagnoses included 25 involutional depressives, 15 schizophrenics, 6 paranoics, and a group of 11 neurotic patients. Chlorprothixene was administered in average doses of 150 to 200 mg/day p.o., Theralen was given in doses of 100 to 200 mg/day p.o., and Prothiadene was given in doses of 150 mg/day p.o. Comparison of the EEG data reveals that the psychopharmacological drugs used show a tendency to synchronize the unsynchronized activity and flat activity of the brain to slow down basal rhythm and increase its amplitude, and to cause slight inhibition of change in sensory stimulation. The differences between the above drugs are quantitative; greatest change was evoked by chlorprothixene, and the least was caused by Prothiadene. The changes observed were the same as those seen with chlorpromazine and other ataractics. The findings indicate a possible use of these drugs in epilepsy and in patients with a tendency toward epileptic seizures.

Medical School, KU
Plzen, Czechoslovakia

826 Hlavatý, J. **Neurotická deprese, její vztahy a vodoléčba. (Neurotic depression, its relation and hydrotherapy.)** Activitas Nervosa Superior, 5:226, 1963.

A group of 46 neurotics was studied to determine whether a dependent relationship of depression to somatic types, especially thermal body types, (K---cold and W---warm), exists. A tendency to depressive association was found in 63.3% of patients of the W body type, and 36.6% of this group did not show depressive association. The converse relationship was found in patients of the K type; 31.2% had depressive association, and 68.7% did not. Warm hydrotherapeutic baths produce a long-lasting decrease, and cold baths produce an extended increase in sensitivity of the vegetative nervous system in both K and W body types. Because of the heightened sensitivity of the sympathetic nervous system in neurotic patients and of the tendency of the organism to normalize values, the application of thermal hydrotherapy in moderate depressive states is recommended, especially in patients of type W. Therefore, pharmacotherapy of hospitalized and ambulatory patients, and patients under home care may be replaced by thermal hydrotherapy.

District Institute of Public Health
Pribram, Czechoslovakia

827 Kümpel, Q., Sokol, I., Topiař, A., & Uhlíř, F. **Pokus o zhodnocení efektivnosti léčby klasickými metodami a ataraktiky u schizofreniků. (The evaluation of efficacy of the treatment of schizophrenia with classical methods and ataractics.)** Activitas Nervosa Superior, 5:194, 1963.

The authors conducted a survey of previous reports and evaluated the results of ataractic therapy in conjunction with psychiatric treatment including electroshock (ES) and insulin shock (IS). Each surveyed report evaluated the frequency of reversions, duration of the first remission, and duration of initial hospitalization. The present authors' conclusions indicated the following: (1) The duration of hospitalization was markedly longer in patients treated by classic methods

in combination with ataractics than in patients using the classic methods (ES and IS) alone. (2) The number of reversions (up to 3 hospitalizations) was equal for all compared groups. (3) Duration of remission based on initial hospitalization was longest for classic therapy (ES and IS). (4) On the basis of the criteria used, it is impossible to evaluate the efficacy of ataractic therapy.

Psychiatric Hospital
Opava, Czechoslovakia

828 Morrison, Ben O. & Bernheim, Edmundo. **Chloral betaine: Evaluation of its sedative-hypnotic properties in geriatric patients.** Journal of the American Geriatrics Soceity, 11(5):439-444, 1963.

A clinical study was made of the sedative and hypnotic properties of chloral betaine in 39 senile, chronically ill patients; 36 similar patients were treated with placebo. Chloral betaine tablets were supplied in two strengths; preparation 1A contained 870 mg chloral betaine (equivalent to 500 mg of chloral hydrate) and preparation 1B contained 435 mg of chloral betaine. Preparation 1A was administered to 6 males and 14 females (average age of 63.5 years). One tablet on retiring was the most common dose. The duration of therapy ranged form 10 days to more than 16 weeks. Insomnia was relieved in all but 2 cases, mental symptoms improved in 6 patients, and in more than half, appetite also improved. No significant side effects were observed. Fifteen females and 4 males (average age of 59.3 years) received preparation 1B. One tablet t.i.d. or q.i.d. was the most common dose. Chloral betaine induced marked relief of anxiety and tension in cases not complicated by psychotic disorder. Even though the drug was administered only in the daytime, 10 patients obtained relief of insomnia. The only side effects were two cases of drowsiness and one case of mild euphoria. Results in the drug-treated groups were significantly superior to those in the placebo group.

Touro Infirmary
New Orleans, Louisiana

829 Stern, Francis H. **Pargyline hydrocloride: A new agent for the control of hypertension and mental depression.** Journal of the American Geriatrics Society, 11(7):670-672, 1963.

A clinical trial of pargyline hydrochloride was conducted among 30 patients (17 females and 13 males) selected from nursing homes. Median age was 67.5 years. In all cases, the diagnosis was depression associated with long-term hypertension (average age of 11.7 years). Before the trial began, all patients were given a physical exam, an EEG, a chest X-ray, and a series of clinical laboratory tests. All medications for hypertension and depression were withheld for 1 week; then placebo was given to all patients for 1 week. Initially, all patients received 25 mg/day pargyline hydrochloride after breakfast. Later trials were made with dosages ranging from 10 to 75 mg/day. At a dose of 50 mg/day, eight patients showed side effects, such as sweating, urinary frequency, nausea, and muscular twitchings; when the amount was increased to 75 mg/day, seven patients showed evidence of orthostatic hypotension and two had severe headaches, nausea, and vomiting. The effective maintenance dose for all patients was eventually adjusted to 25 to 50 mg/day. Improvement in depression did not occur until about 3 months and was most marked at the end of 4 months. The results show that a proper maintenance dose of pargyline hydrochloride is effective in reducing high blood pressure and in controlling hypertensive symptoms and associated mental depression.

332 South 21st Street
Philadelphia, Pennsylvania

830 Hollister, Leo E. & Motzenbecker, Francis P. **Haloperidol in schizophrenic reactions.** Journal of Neuropsychiatry, 4(6): 386-387, 1963.

The efficacy of haloperidol was tested in 42 schizophrenics, most of whom were chronic, whose mean age was 33 years and whose mean duration of illness was 8 years. Comparative evaluations were made after a 3-month treatment with 4 to 40 mg of the drug, median dose being 15 mg. Fifteen patients obtained clinically significant degrees of improvement, but only occasionally did it appear specific for this drug. In 29 patients, extrapyramidal disorders that were often severe and hard to control occurred, including akathisia in 21, Parkinson syndrome in 9, and dystonic reactions in 3. Of these patients, 22 developed side effects on doses of 12 mg or less. Other side effects were drowsiness, constipation, and, in two patients, bladder and bowel incontinence. It is concluded that haloperidol is an effective drug, but clinical results are no better than those of commonly used drugs, and are probably less than re-

sults that might be obtained with potent phenothiazine tranquilizers having less troublesome side reactions.

Veterans Administration Hospital
Palo Alto, California

831 Warter, J. Pennington, Schultz, Ward M., & Brady, James L. Oral therapy of skeletal muscle spasm with combined orphenadrine–fluphenazine. Journal of New Drugs, 3(5):317–320, 1963.

This study compares the effects of treatment with tablets of combined orphenadrine–fluphenazine and of orphenadrine alone in 111 patients (14 to 71 years old) with acute and chronic musculoskeletal and neuromuscular disorders. The combination tablet contained 100 mg orphenadrine citrate and 0.5 mg fluphenazine dihydrochloride; the control tablet contained 100 mg orphenadrine citrate. Both preparations were given t.i.d. Exploratory trials lasting from 4 to 30 days of orphenadrine–fluphenazine therapy were made in the first 47 patients admitted to study; in 11 of these, selected at random, subsequent trials of orphenadrine alone were also made. The results of these trials, in which 36 of the 47 patients on the combination had complete or marked relief of painful spasm or stiffness of affected muscles, 9 had moderate control of muscle spasm, and 2 had slight improvement, indicated that the combined drugs were more effective than orphenadrine alone (of the 11 patients, 2 had marked relief, 2 moderate relief, 4 slight improvement, and 3 no improvement). In the next 64 patients, a double-blind comparison of the two preparations was made. Moderate to complete relief of skeletal muscle spasm was observed in 84% of 63 trials of orphenadrine–fluphenazine and in 27% of 47 trials of orphenadrine alone. No untoward effects of clinical significance were noted during treatment with either medication. The capacity of small doses of fluphenazine to alleviate emotional and somatic symptoms of anxiety may explain the markedly different effectiveness of the combination treatment; fluphenazine is also capable of enhancing the pharmacologic effects of some drugs.

Westfield Orthopedic Group
Westfield, New Jersey

832 Batterman, Robert C., Mouratoff, George J., & Kaufman, Jerome E. **Comparative treatment of the psychoneurotic reactive-type anxiety state with fluphenazine and chlordiazepoxide.** Journal of New Drugs, 3(5):297–301, 1963.

Fluphenazine dihydrochloride, chlordiazepoxide, and placebo were evaluated by a blind technique as tranquilizers for the treatment of 91 patients (63 female and 28 male) with psychoneurotic reactive-type anxiety. Fluphenazine dihydrochloride, 1 mg t.i.d., was effective in 52.6% of the trials as compared with 43.0% for placebo therapy and 54.3% for chlordiazepoxide, 10 mg.q.i.d. All were given in capsule form. The observed difference in the effectiveness of the two drugs was not significant. The prolonged action of fluphenazine was demonstrated by alternate placebo administration. With the dosage of fluphenazine dihydrochloride employed in this study, effective control of daytime anxiety symptoms is possible with minimal likelihood of drowsiness. The occurrence of adverse effects was minimal with all three preparations. Five patients noted side reactions (weakness, dizziness, and one case of drowsiness) with fluphenazine, seven patients noted side reactions (sluggishness, nausea, and drowsiness) with chlordiazepoxide, and three patients noted side reactions (drowsiness, anorexia, and grogginess) with placebo. Both fluphenazine and chlordiazepoxide are effective, mild tranquilizing agents for the psychoneurotic reactive-type patient.

Foundation for Clinical Pharmacology, Inc.
Berkeley, California

833 Kissin, Benjamin, Tripp, Clarence A., Fluckiger, Fritz A., & Weinberg, George H. **Effect of ataractic drugs on motor control in acute hospitalized psychiatric patients.** Journal of Neuropsychiatry, 4(6): 409–412, 1963.

Four ataractic drugs (chlorpromazine, meprobamate, chlordiazepoxide, and sodium pentobarbital) and a placebo (vitamin C) were administered in simple rotation to 102 male acute hospitalized psychiatric patients, in order to study whether there was any significant improvement in the level of motor control. The graphodyne, an electro-oscillograph, was used to measure handwriting pressure. The patients were instructed to write as lightly as possible; therefore, the lower the pressure value, the higher the degree of motor control. Graphodyne patterns were taken before and 1 hour after administration of one of the following: 50 mg chlorpromazine, 800 mg meprobamate, 50 mg chlordiazepoxide, 100 mg sodium pentobarbital, or 50 mg placebo. There were 20 pa-

tients in each drug group, and 22 patients, in the placebo group. The results obtained confirm the clinical impression that the four drugs in the dosages used are effective in ameliorating the disruptive effects of psychiatric stress on psychomotor performance. Improvement in motor control in each drug was significant at $p < 0.01$; with placebo, there was no significant change. This technique may be valuable for differentiating between significantly effective and noneffective tranquilizers, as well as between significantly effective and noneffective dosages of effective tranquilizers.

State University of New York
Brooklyn, New York

834 Ancona, V. Charles & Caloza, Dionisio, Jr. **Observations on the effectiveness of arginine and glutamate therapy in delirium tremens.** Journal of Neuropsychiatry, 4(6): 369-374, 1963.

The effects of the administration of L-arginine--L-glutamate (LALG) and/or L-arginine monohydrochloride (LAMH) in the treatment of 25 patients (22 male and 3 female, from 31 to 69 years old) with typical delirium tremens were evaluated. Seventeen patients were treated with LALG, seven with LAMH, and one with both. Initial dose was 25 g of either drug, diluted in 1,000 ml of 10% dextrose in water, given by i.v. infusion at a rate of 30 to 40 drops per minute; a single treatment lasted for from 2-$\frac{1}{2}$ to 3 hours. Total doses were generally 75 or 100 g. The use of paraldehyde, tranquilizers, alcohol, and sedation was eliminated in the course of therapy. Nineteen case histories are given. All 25 patients responded satisfactorily to therapy. All except one were asymptomatic within 72 hours: 7 patients within 24 hours and 14 patients within 12 hours. The rapid recovery of these patients makes them amenable to a more effective and adequate treatment of their systemic and nutritional deficiencies. No complications from the use of either drug have arisen. This treatment precludes the need for prolonged and difficult nursing and mental care, and prevents the occurrence of severe and fatal complications associated with the syndrome.

St. Clare's Hospital
New York, New York

835 Orlansky, George J. & Osterheld, Roger G. **The use of a synthetic anabolic, methandrostenolone, as an adjuvant in treatment of epilepsy.** Journal of Neuropsychiatry, 4(6):366-368, 1963.

Because of previous favorable reports on methandrostenolone---a synthetic tissue-building hormone of low androgenicity---it was tested to ascertain if it could be used in patients with serious emotional disturbances and behavior problems secondary to epilepsy. A group of 51 patients, male and female, (12 to 66 years old) with IQ's of about 30 were chosen for this double-blind study. All patients had been taking 4.5 gr/day of anticonvulsant diphenylhydantoin sodium for several years; in addition, 26 were given 10 mg/day of methandrostenolone and 25 were given placebo over a period of 3 months. Other medications that the patients had been taking were continued. No significant differences in behavior, emotional disturbance, or hyperactivity were noted between the two groups. There was an increase in hair growth (hypertrichosis) in males only in both groups, which could be attributed to the anticonvulsant diphenylhydantoin sodium. Methandrostenolone in doses of 10 mg or more daily is of no value in controlling the emotional disturbances or hyperactivity seen with epilepsy.

Monson State Hospital
Palmer, Massachusetts

836 Engelhardt, David, Freedman, Norbert, & Mann, David. **The influence of previous hospitalization on the clinical course of psychopharmacologically treated schizophrenic outpatients.** Comprehensive Psychiatry, 4(5):337-342, 1963.

The first 310 consecutive admissions to a research clinic (who remained in treatment for at least 3 weeks) were selected for study. Patients from both sexes (age range, 19 to 44 years) with a primary diagnosis of chronic schizophrenia were randomly assigned to chlorpromazine (mean dose, 150 mg daily), promazine (mean dose, 200 mg daily), or placebo treatment groups. Conditions were double-blind; only the strength of the capsule was known to physicians. Of the 310 patients, 163 had either never been hospitalized or had a total hospitalization of less that 3 months. The remaining 147 patients were characterized by previous hospitalization with a median duration of 1 year. The two groups were studied in terms of hospitalization rate and improvement in social behavior. Social improvement was determined by a 15-item social pathology rating scale administered to a close relative at the end of 6 months of treatment. For patients with a history of previous hospitalization and prone to rehospitalization, active drug therapy significantly reduces this tendency. For patients not previously hospitalized and not

prone to hospitalization, active drug therapy tended to improve the quality of social behavior. In another preliminary study, it was found that history of hospitalization was not related to the various diagnostic subgroups among the schizophrenic population nor was it related to severity of psychotic symptomatology.

State University of New York
Brooklyn, New York

837 Belmont, Ira, Pollack, Max, Willner, Arthur, Klein, Donald, & Fink, Max. **The effects of imipramine and chlorpromazine on perceptual analytic ability, perceptual responsivity and memory as revealed in Rorschach responses.** Journal of Nervous and Mental Disease, 137(1):42-50, 1963.

Fifty-four psychiatric inpatients with a variety of diagnoses were randomly assigned to two drug groups (chlorpromazine and imipramine) and to a placebo comparison group in a double-blind study to determine drug effects on perceptual-analytic ability, perceptual responsivity, and recall memory, as revealed in Rorschach responses. Drugs and placebo were administered on a fixed-dosage schedule in a masked vehicle over a five-week period in increasing concentrations up to a maximum of 1,200 mg of chlorpromazine (with 1.25 percent procyclidine added) and 300 mg of imipramine. Schizophrenic patients exhibited drug-related changes that were not shown by nonschizophrenic patients. Both drug groups of schizophrenic patients exhibited changes in a similar direction. Perceptual responsiveness to multiple visual stimuli increased, and perceptual-analytic ability and memory for self-structured visual percepts improved. The analysis of the data led to the conclusion that when the effects of drugs are explored, it is necessary to examine the psychological functions exhibited in relation to the situational determinants of behavior. (Author abstract, edited)

Hillside Hospital
Glen Oaks, New York

838 Alexander, Fred, Curtis, George C., III, Sprince, Herbert, & Crosley, Archer P., Jr. **L-methionine and L-tryptophan feedings in non-psychotic and schizophrenic patients with and without tranylcypromine.** Journal of Nervous and Mental Disease, 137(2):135-142, 1963.

The effect of L-tryptophan and L-methionine administered concomitantly with an MAO inhibitor was studied in six chronic schizophrenics and in two nonpsychotic psychiatric inpatients (20 to 55 years old). All were free from any other illness and were able to cooperate. Patients were carefully selected according to defined criteria; all received a series of physical, psychiatric, and laboratory tests prior to final selection. Every week for 6 weeks, each patient received a combination of medications in accordance with a Latin-square, single-blind format. Either 5 g of L-tryptophan or 6.6 g of L-methionine was administered t.i.d., with or without 10 mg of tranylcypromine, also given t.i.d. There was a 7-day drug-free period after the third week. Of the six schizophrenic patients, at least three showed evidence of drowsiness, lethargy, and fatigue. A series of responses peculiar to each individual, including adrenergic symptoms, an increase in psychotic thinking, and somatic complaints, were noted. The combination of tranylcypromine plus L-methionine produced the most potent clinical effects in at least one patient. One typical case study is presented. The nonpsychotic patients showed behavioral changes similar to those of the schizophrenic group. The combination of tranylcypromine and L-methionine was again followed by a clinical reaction. Laboratory analyses showed evidence of systemic acidosis, particularly in patients receiving L-methionine.

Pennsylvania Hospital
Philadelphia, Pennsylvania

839 Engelhardt, David M., Freedman, Norbert, Hankoff, Leon D., Mann, David, & Margolis, Reuben. **Long term drug-induced symptom modification in schizophrenic outpatients.** Journal of Nervous and Mental Disease, 137(3):231-241, 1963.

The clinical course of two groups, each consisting of 12 chronic schizophrenic outpatients receiving chlorpromazine and placebo treatment, respectively, was studied. The groups were matched on a case by case basis for severity of psychotic symptomatology at intake. There were 16 males and 8 females (mean age of 30.2 years); 15 of the patients had a previous history of hospitalization; 19 patients were white and 5 were Negro. The range of clinic attendance was from 12 to 51 months, with an average of 27.1 months. It was observed that, compared with placebo, the chlorpromazine-treated patients showed significant reduction of psychotic symptomatology within the first 3 months of treatment; this reduction was further accentuated

at 12 months and tended to be sustained thereafter; furthermore, there was greater stability of the rate of symptom modification over the entire span of treatment. The changes in symptomatology were predominantly in the area of paranoid ideation, structural thought disorder, withdrawal, and feelings of self-depreciation. The clinical results supported the conclusion that prolonged chlorpromazine treatment of chronic schizophrenic outpatients is associated with sustained symptom modification for a period in excess of 2 years.

State University of New York
Brooklyn, New York

840 Osborne, Robert G., Tunakan, Bulent, & Barmore, John. **Anesthetic agent in electro-convulsive therapy: A controlled comparison.** Journal of Nervous and Mental Disease, 137(3):297-300, 1963.

A double-blind study was devised to compare methohexital sodium and thiopental sodium as anesthetic agents in succinylcholine chloride-modified ECT. Nineteen consecutive inpatients (18 to 72 years old) referred to a state psychiatric institute received a total of 130 electroconvulsive treatments (2 to 16 treatments per patient). Treatment routine was as follows: pretreatment with 0.4 mg atropine sulfate 30 minutes prior to ECT, slow i.v. injection of anesthetic agent, succinylcholine chloride i.v., electroconvulsive stimulus applied as soon as fibrillary twitchings occurred, oxygen given until adequate oxygenation was restored, and patient transferred to the recovery room. The amount of anesthetic agent used varied with each patient. Methohexital sodium was administered i.v. as a 1 percent solution with a dosage range from 90 to 140 mg. Thiopental sodium was administered i.v. as a 2.5 percent solution with a dosage range of 200 to 350 mg. The dosage of succinylcholine chloride ranged from 15 to 40 mg. The average duration of anesthesia (between administration and first verbal response) with thiopental sodium was 10 minutes and 36 seconds; with methohexital sodium, it was 8 minutes. The average duration of anesthesia from administration to unassisted ambultation was also longer with thiopental sodium. Recovery was more rapid from methohexital sodium. The duration of apnea varied from patient to patient and with the amount of succinylcholine given. The average length of apnea with methohexital was 2 minutes and 33 seconds; the most common side effect of methohexital was hiccoughs (7 of 72 treatments), and one case of nausea was reported. Postanesthetic nausea, vomiting, and confusion occurred in 18 of 72 treatments with thiopental.

University of Nebraska College of Medicine
Omaha, Nebraska

841 Gross, Martin, Hitchman, Irene, Reeves, Walter P., Lawrence, Jordan, & Bacon, E. Faye. **The repetitive administration of two psychological tests during withdrawal from ataractic drugs.** Journal of Nervous and Mental Disease, 137(6):574-576, 1963.

A double-blind study of the effects of withdrawal of ataractic medication was conducted among outpatients of a state hospital. Chronic psychotic patients (144) released from the hospital were continued on one of the following drugs: chlorpromazine, perphenazine, prochlorperazine, promazine, or reserpine in unidentifiable capsules or tablets. After an average observation period of 4.3 months, during which regular observations were made, the patients were randomly divided into groups. One group was continued on the same medication; the other group received the same number of capsules as before, but the drug content was gradually reduced until it was replaced entirely by placebo. Every 3 months, and upon relapse, all patients were evaluated by a psychiatrist, a psychologist, and a social worker. The two psychological tests used were the figure-drawing test and a revision of the standard Myokinetic Psychodiagnosis (MKP). Based on the standards described, there was no difference between prerelapse and relapse drawings in 14 of 29 sets of drawings from relapsed patients. In eight cases, the relapse drawing was worse, and in seven cases, it was better than the prerelapse drawing. Similarly, it was found that none of the 21 items used from the MKP could reliably predict relapse.

Springfield State Hospital
Sykesville, Maryland

842 Marks, John. **Predrug behavior as a predictor of response to phenothiazines among schizophrenics.** Journal of Nervous and Mental Disease, 137(6):597-601, 1963.

Data from a large-scale cooperative trial of five phenothiazines and phenobarbital with schizophrenic patients were analyzed, in order to determine what predrug patterns of behavior predicted responsiveness to the individual drugs. Individual responsiveness to the four drugs that showed the greatest effectiveness---chlorpromazine, triflupromazine, perphenazine, and prochlorperazine---was computed, using a score that allowed for individual differences in initial scores, as

well as comparability between the four drug groups. These responsiveness scores were then correlated with Multidimensional Rating Scale scores, which were made on the study subjects before drug administration was started. Responsiveness to chlorpromazine is associated with cooperativeness, to perphenazine with sociability, to prochlorperazine with activity level, and to trifluproma-zine with anxiety and tension. A comparison with the data from the Spring Grove comparative phenothiazine study suggests that most of these correlations are stable. (Author abstract, edited)

Mental Health Research Institute
Fort Steilacoom, Washington

843 Liske, E. & Forster, Francis M. **Clinical evaluation of the anticonvulsant effects of sulthiame.** Journal of New Drugs, 3(1):32-36, 1963.

The anticonvulsant effects of sulthiame were evaluated in 53 epileptic patients, ranging in age from 26 months to 56 years. The drug was added to the previously unsatisfactory anticonvulsant regimen, with the usual dose being 200 mg t.i.d. for adults and smaller doses for children; duration of therapy ranged from 1 day to 1 year (average, 6.45 months). Sulthiame therapy reduced seizures in 31 patients and increased seizure frequency in 3; there was no change in 19 patients. Psychomotor and grand mal seizures were more favorably affected than were focal or petil mal seizures. Failure to control seizures was not due to inadequate dosage, since patients whose seizures were not controlled received higher dosage levels. The following side effects occurred: acute psychotic episodes (6 patients), sensorial clouding (9), paresthesia (7), hyperpnea with tachypnia (13), and papilledema with paraphasia and visual illusions (1).

University of Wisconsin Medical Center
Madison, Wisconsin

844 Prange, Arthur J., Jr., Cochrane, Carl M., Abse, D. W., & Boswell, John I. **A double blind clinical trial of chlorpromazine and reserpine in acute mental disturbance.** Journal of New Drugs, 3(2):85-95, 1963.

The effects of lactose, opium, reserpine, and chlorpromazine on acute psychiatric patients, psychotic and nonpsychotic, were studied in a double-blind, objective measure design. Reserpine patients received 8 mg for 2 days, then 4 mg daily; chlorpromazine patients received 600 mg for 2 days, then 300 mg daily; the opium patients received 400 mg for 2 days, then 200 mg daily. Before medication, and daily thereafter, one nurse on each shift described the patient's behavior by filling out a 67-item checklist. The resident filled out a weekly anxiety-rating score. A psychologist gave the MMPI and the Purdue Pegboard test weekly. For data analysis, patients were divided into psychotic and nonpsychotic groups. Too few nonpsychotics received chlorpromazine for valid conclusions, so results are based on the use of lactose, opium, and reserpine. In the psychotic group, tranquilizers were superior to placebo and opium. In the nonpsychotic group, reserpine was no more effective than opium or lactose. Methods of data analysis are described in detail.

University of North Carolina School of Medicine
Chapel Hill, North Carolina

845 Liske, E. & Forster, Francis M. **Clinical study of a new benzodiazepine as an anticonvulsant agent.** Journal of New Drugs, 3(4):241-244, 1963.

A new analog of chlordiazepoxide, 7-nitro-5-phenyl-3H-1-,4-benzodiazepin-2(1H)-one, referred to herein as LA-1, was tested for anticonvulsant properties in 50 epileptic patients with various types of poorly controlled seizures. Patients ranging in age from 4 months to 55 years (mean, 17.5 years) and weighing from 7.73 to 90.9 kg (mean, 49.3 kg) were treated for 3 days to 16 months (mean, 5.45 months) with LA-1. The usual adult starting dose was 5 mg t.i.d., and in a 5-year-old child, 2 mg t.i.d.; subsequent dosage varied from 0.07 to 1.09 mg/kg body weight. Thirty patients had some reduction in at least one type of seizure; five had some worsening in one type; and 16 had no change in seizure frequencey. (The total, 51, is greater than the number of patients studied, since one patient had a worsening of grand mal and a reduction of petit mal seizures.) Twelve patients complained of the following side effects: impaired concentration (3), drowsiness (2), drowsiness and staggering (2), and worsening of seizures (5). One patient developed leukopenia. The LA-1 was most effective in treating myoclonic, temporal lobe, and petit mal seizures.

University of Wisconsin Medical Center
Madison, Wisconsin

846 Wessler, Margaret M. & Kahn, Virginia L. **Can the chronic schizophrenic patient remain in the community?: A follow-up study of twenty-four long-term hospitalized patients returned to the community.** Journal of Nervous and Mental Disease, 136(5):455-463, 1963.

A followup study was made on 24 patients, from an original group of 115 chronic schizophrenics, who, though profoundly ill, had remained out of the hospital for 6 months to 3 years, in order to determine what factors enabled them to remain in the community. Eighteen patients had been in the community continuously since discharge; six patients had been rehospitalized at one time or other. The study is discussed in five parts: (1) a description of the patients; (2) an evaluation of the level of social adjustment attained after discharge; (3) an examination of factors that may have helped the 18 patients to remain out of the hospital, such as intensive social therapy, drugs, and family attitudes; (4) an attempt to evaluate the factors leading to rehospitalization of the six patients to ascertain why they failed to remain in the community; and (5) a comparison of the 18 successful patients with the six who were rehospitalized. Three factors were found to be necessary for a long-time hospitalized patient to remain in the community: (1) sustained family interest; (2) continued drug therapy; and (3) continued availability and use of psychiatric and social therapies during the period of discharge.

Massachusetts Mental Health Center
Boston, Massachusetts

847 Ayme, J., Paillot, M., Ostaptzeff, G., Ostaptzeff, M., & Teboul, R. **Remarque sur l'utilisation corrélative de l'imipramine et des thérapeutiques institutionnelles. (Observations on the correlative use of imipramine and institutional therapeutic measures.)** Annales Médico-Psychologiques, 2:265-271, 1963

The aim of this work is to attempt to show the effects of imipramine on hospitalized schizophrenics in adjunct with chemotherapy and sociotherapy. Imipramine was given in tablet form, totaling 75 to 300 mg/day, to 10 catatonic hebephrenics and 4 delirious paranoic patients (mainly with verbal delirium). Adjunct medication included meprobamate and levomepromazine. Duration of treatment was 2 to 6 months, and was conducted under regular EEG control. The setting consisted of a cooperative club of 334 hospitalized patients in which the patients regulated the mechanism of the social life, ergotherapy, and finances of the club. This setting shows an interest in the patient and demands activity on his part, and the patient on imipramine brings much to the setting, such as oscillating it between organizational and psychodramatic poles. The patients are asked to make practical plans for the immediate future and to assume responsibilities. A return to an autistic attitude may be seen at the beginning of the treatment, but such regressions are rare after 2 or 3 months on imipramine. Although imipramine does not influence fundamental processes it does enable greater penetration of the "critical distance," or "private space" of the schizophrenic. The use of imipramine with schizophrenics in an institutional setting, however, appears to present certain dangers.

(No address)

848 **Un nouveau neuroleptique: La Propériciazine. (A new neuroleptic: Propériciazine.)** Journal de Médecine de Bordeaux, 140:738, 1963.

Propericiazine is a new phenothiazine derivative with effects resembling those of chlorpromazine, but at much lower doses. It was administered to 293 patients (238 female and 55 male, age not indicated) at the rate of 30 to 40 mg/day (1/4 of the dosage in the A.M. and 3/4 of the dosage in the P.M.). The latent period ranged from several days to several weeks. The results obtained were as follows: 76% good results in neurotic psychopathic cases; 58% improvements in debilitated and epileptic psychopathic cases; 60% improvements in acute psychoses; 44% success in neuroses; 30% good results in schizophrenics; 46% improvements in chronic psychoses; and 3 of 19 cases of senile dementia showed improvement. Digestive tolerance was good, as long as dosage was not exaggerated. There was no local irritation in i.v. administration. Side effects were sleepiness and lassitude, plus slight extrapyramidal manifestations. Parkinsonian syndrome appeared in 10% of the cases, which was more pronounced in 4 cases (beginning with 100-mg dose). This was easily corrected by antiparkinsonian drugs. Hypotension was observed in several cases, and generalized edema appeared in one case. The authors estimate that propericiazine is a "comfortable" medication, useful as an alternate to known neuroleptics and as post-treatment. Remarkable results have been obtained often in reduction of impulsiveness, aggression, and antisocial reactions.

(No address)

849 Ryan, Robert E **Myalgia of the head and its treatment with diazepam.** Headache, 3:63-66, 1963.

Myalgia of the head, a manifestation of physical allergy in people exceptionally sensitive to sudden changes in temperature, is described, and its etiology is discussed. Past treatment affording relief consisted of a nicotinic acid--mephenesin combination, methocarbamol, or methopholine--a new analgesic. Fifty myalgic patients treated with diazepam, a benzodiazepine derivative, received 1 tablet (2 mg) t.i.d. Of these, 20 had excellent relief of pain, 15 had good relief, 6 had good relief, 6 had some relief, and 9 had no relief. Drowsiness was the only side effect encountered. Four of the 50 patients (8%) experienced drowsiness, but only 2 of these wished to discontinue the drug because of the drowsiness. Results also show that this new drug has a good margin of safety, and it gave little indication of preventing patients from performing their usual functions. The drug was chosen for its skeletal-muscle relaxing properties because muscular spasm may potentiate and aggravate symptoms of myalgia of the head.

St. Louis University
St. Louis, Missouri

850 Lai, G. **Stimulation et sédation le traitement des états dépressifs.** (Stimulation and sedation in the treatment of depressive states.) Psychopharmacologia, 4: 206-220, 1963.

The principles of stimulation and sedation by psychotropic drugs are reviewed, and the results of treatment of 104 depressed patients with amitriptyline are discussed. The patients were given 150 mg i.m. for 10 days, followed by 150 or 200 mg in tablet form, and decreasing to 75 mg after an average of 2 weeks. The above dosage appears to be optimal, and increased dosage does not produce parallel clinical improvement. The positive effects of amitriptyline include hyperaffectivity and agitation, and the negative effects include hypoaffectivity and motor inhibition. Of the 104 patients, amitriptyline produced complete remission in 37%, incomplete remission in 20%, improvement in 13%, no change in 20%, and aggravation in 10% of the patients. Good improvement was obtained chiefly in patients having a predominance of positive effects which, if they occur, appear within the first few days. The main side effects were drying of mucosa, some difficulties of accommodation, and constipation. Amitriptyline is well tolerated, and produces no undesirable cardiovascular effects. To avoid regression, it is recommended that a maintenance dosage of 30 to 75 mg/day be taken for several months after discharge. The quantitative effects of amitriptyline are between those of chlorpromazine and imipramine; it has the specific sedative property of chlorpromazine and the stimulating characteristic of imipramine.

Clinique Psychiatrique
Universitaire de Lausanne
Lausanne, Switzerland

851 Appleton, William. **Massive doses of chlorpromazine.** Archives of General Psychiatry, 9:586-592, 1963.

Because 25 of a total of 300 patients treated with chlorpromazine over a 2-year period at a teaching (psychiatric) hospital received more than 1,500 mg daily, a study was made of the effectiveness of massive therapy and of the types of patients for which it is best suited. It was found that two-thirds of patients termed overactive or destructive, and a similar number of those observed to be withdrawn, were successfully treated and discharged following the use of massive doses of chlorpromazine. Massive therapy did not improve either the discharge rate or the behavior of assaultive patients. After failure of massive drug therapy, ECT was successfully employed with assaultive or overactive-destructive patients, but not with withdrawn patients. An increase of parkinsonian and anticholinergic side effects were encountered with massive doses, but convulsions and coma were found only if high dosage was achieved too rapidly. Three of eight patients who received over 1,500 mg daily in less than 3 days from the onset of therapy had convulsions or coma.

Massachusetts Mental Health Center
Boston 15, Massachusetts

852 Destounis, Nicholas. **Enuresis and imipramine.** American Journal of Psychiatry, 119:893, 1963.

A case report of a 15-year-old boy with a history of enuresis accompanied by depression and suicidal preoccupation is presented. After the second nightly dose of 50 mg imipramine, the bed wetting ceased, and the clinical picture of depression disappeared within a week. After 2 months of supportive psychotherapy, the boy was free of the enuresis and of all the other original symptoms.

University Avenue
Halifax, Nova Scotia

853 McCabe, William S. & Habovick, Joseph A. **Thorazine as an epileptogenic agent.** American Journal of Psychiatry, 120: 595-597, 1963.

To clear up the question as to whether chlorpromazine has epileptogenic properties, 26 convulsive patients who were already on anticonvulsant medication were placed on sizable daily doses of chlorpromazine (dosage not given). Observations covered 5 months. The hospital records for the months of February, March, and April were compared with those of May and June when the chlorpromazine was added to the daily regime. Only patients with grand mal seizure were considered. Of the 26 patients, none had severe seizures while on chlorpromazine as compared to 3 patients who were not on chlorpromazine. One patient showed an increase of seizures, but these were changed from severe to mild. Four patients had reduction of seizures. The anticonvulsants used were diphenylhydantoin sodium, promidone, and phenobarbital, alone and in combination. The findings indicate that chlorpromazine is not only nonepileptogenic, but actually reduced the number of seizures as well as their severity. This may be explained by reduction of the emotional portion of the convulsive threshold by chlorpromazine. An incidental finding was a marked reduction in the amount of chlorpromazine needed to control behavior in these patients, indicating a potential effect between diphenylhydantoin sodium and promidone when used with chlorpromazine. There is no potential effect on phenobarbital. Many of the "pure" schizophrenic patients showed continued improved behavior with diphenylhydantoin sodium and promidone, indicating that, at least in some cases, schizophrenia is "organically caused."

Woodville State Hospital
Woodville, Pennsylvania

854 Hollister, Leo E., Overall, John E., Meyer, Fred, & Shelton, Jack. **Perphenazine combined with amitryptiline in newly admitted schizophrenics.** American Journal of Psychiatry, 120:591-592, 1963.

A combination of perphenazine (56 mg daily) and amitryptiline (175 mg daily) was tested in 60 schizophrenic patients. Clinical progress was rated by joint psychiatric interviews with two raters who independently assessed patients on the Brief Psychiatric Rating Scale (BPRS) and the Inpatient Multidimensional Psychiatric Scale at the beginning and end of treatment. Score changes on both scales showed highly significant improvement. Patients showed the following side effects: drowsiness (7 patients), agitation (5), dry mouth (10), delayed urination (2), and acute urinary retention (1). Extrapyramidal symptoms were not common, probably due to the anticholinergic effects of amitryptiline. Despite the excellent results of this combination, there was no evidence that amitryptiline added anything to the expected effects of perphenazine alone.

Veterans' Administration Hospital
Palo Alto, California

855 Remington, Frederick B. **The use of chlordiazepoxide (Librium) in the barbiturate abstinence syndrome.** American Journal of Psychiatry, 120:402-403, 1963.

The history of a 28-year-old woman who was withdrawn from a 2-year barbiturate addiction with the assistance of chlordiazepoxide is presented. Her intake had amounted to more than 600 mg pentobarbital daily. The patient was maintained on her admission dosage for 3 days, which was then reduced at the rate of 25 mg/day. Typical signs of the abstinence syndrome began to appear in 2 to 3 days. Chlordiazepoxide doses were begun at 10 mg q.i d., and over a 3-day period, were increased to 100 mg daily. At the 100-mg level, abstinence symptoms were well controlled. Anxiety and associated fears decreased, appetite and sleep improved, and the patient became generally more comfortable. The patient was maintained on chlordiazepoxide until she had been off all barbiturates for 2 weeks, after which the drug was discontinued over an 8-day period. The rebound symptoms that occurred lasted only a few days and were handled by psychotherapy.

Four Winds Hospital
Katonah, New York

856 **Treatment of enuresis with imipramine.** American Journal of Psychiatry, 120: 196, 1963.

A clinical note in the November 1962 "American Journal of Psychiatry" reports poor results from treating enuresis in children and adults with relatively small doses of imipramine. A reply to this article suggested that larger doses of the drug would produce satisfactory results. The author of the clinical note reports that a second series of experiments is being run at higher doses.

(No address)

857 Jarecki, Henry G. **Combined amitriptyline and phenelzine poisoning.** American Journal of Psychiatry, 120:189, 1963.

A case history is presented of poisoning by amitriptyline (which resembles imipramine structurally and chemically) combined with the MAO inhibitor phenelzine. A woman ingested 180 mg phenelzine, 800 mg amitriptyline, and a small amount of acetylsalicylic acid and chlorpheniramine in an attempted suicide. She had been taking 150 mg amitriptyline for 12 weeks prior to the suicide attempt. The patient displayed mild disorientation, drowsiness, bilateral Babinski signs, hypertension (typical of MAO-inhibitor overdosage) alternating with hypotension, urinary retention, and elevation of temperature. Symptoms disappeared on the third day after hospitalization. Caution is urged in prescribing combined amitriptyline and phenelzine.

Grace-New Haven Community Hospital
New Haven, Connecticut

858 Schneider, Daniel. **Notes d'emploi à l'usage du praticien au sujet du Librium en psychiatrie ambulatoire. (Explanatory notes for the use of the practitioner on the subject of Librium in ambulatory psychiatry.)** Strasbourg Medical, 13:422-426, 1962.

A clinical study was done of the effects of chlordiazepoxide on 10 dispensary patients, 6 hospitalized acute neurotics, and 40 ambulatory private patients (age not mentioned). Initial experience shows that chlordiazepoxide is ineffective in cases in which neurotic anxiety is connected with material insecurity (dispensary). Three of the hospital cases of obsessive psychoneurosis accompanied by delirium were not favorably influenced, and chronic phobic neurosis in the three other hospital cases was aggravated by depressive evolution, necessitating major neuroleptic treatment. The effect was most positive in ambulatory psychiatric patients, producing emotional relaxation, existential dedramatization, facilitation of relation, and change in neurotic attitude. The drug produced 16 provisional cures, improvement of 21 patients, and no change in 7. The following clinical advice may be proposed: (1) Insecurity must not be aroused in the patient by bringing up a somatic problem, and practitioner--specialist cooperation should be established. (2) On the technique level, drugs with contradictory action should not be combined; application should be limited to localized neurotic cases; chlordiazepoxide should not be used in psychoses; and the drug should be accompanied by psychotherapy. (3) In connection with the method of application, psychopharmacological conditioning should be avoided because the aim is to gain access to the patient's conscience. The hierarchy of symptoms affected is anxiety, phobic doubt, and modification of emotional tension.

Dispensaire d'Hygiène Mentale
Mulhouse, France

859 Adelson, Daniel & Turner, Ann. **A note on the relation of somatotype to outcome after phenothiazine therapy in chronic schizophrenic patients.** Journal of Nervous and Mental Disease, 137(3):242-245, 1963.

Somatotypes, using Sheldon's typology, were obtained for 58 patients from a larger group of patients treated with phenothiazines in a controlled, double-blind investigation of the effectiveness of ataraxics in chronic schizophrenic men and women. The somatotypes were then classified into seven categories: (1) endomorphy predominant; (2) mesomorphy predominant at the 5 to 5-$\frac{1}{2}$ level (men) and 4 to 5 level (women); (3) ectomorphy predominant; (4) balanced somatotypes---all components at midrange; (5) low total somatotypes; (6) low mesomorphy; and (7) mesomorphy predominant at the 5-$\frac{1}{2}$ to 7 level (men). Analysis showed that 73% of patients in Category 2 passed hospital conferences with members of the hospital staff, and were considered ready for hospital leave. A chi-square test comparing Category 2 with other categories was significant ($p < 0.01$). Seven out of seven women patients in this category passed conference. An addendum describing Shelton's somatotyping procedure is included.

University of California Medical Center
San Francisco, California

860 Krakowski, Adam J. **Chlorprothixene in private psychiatric practice: A one year follow-up.** Journal of New Drugs, 3(2): 110-114, 1963.

To assess the long-range development in a group of patients previously treated with chlorprothixene, 16 unimproved and 32 improved (15 complete remission and 17 marked improvement) patients were reevaluated approximately 1 year following the original drug study. Of those who improved, 2 relapsed (both schizophrenics), 1 died after relapse (acute brain syndrome), 14 remained improved without medication, and 15 remained improved with continued chlorprothixene medications. Those psychotics who still received drug treatment continued to show improvement, with four cases of marked improvement reach-

ing complete recovery. Side reactions in the improved group were practically nonexistent, and no toxic reactions were observed despite an average of 15.4-months' therapy on an average daily maintenance dosage of 150 mg of chlorprothixene.

Champlain Valley and Physicians Hospitals
Plattsburgh, New York

861 Hudgens, R. W. Psychiatric inpatients at a teaching hospital. Archives of General Psychiatry, 9:384-389, 1963.

An inquiry into events preceding and during hospital treatment of 35 patients (12 males and 23 females) was made in an attempt to uncover factors bringing about admission, to examine therapeutically significant events, and to understand changes in clinical status with reference to the reasons for admission and to events during hospital treatment. In classifying patients by major symptoms, 17 had psychoneurotic disorders, 10 were psychotic, 5 had personality pattern or trait disturbances, 2 had adjustment reactions of adolescents, and 1 had a psychophysiologic disorder. Twenty-nine patients were treated with psychotherapy alone, three by psychotherapy and ataractic drugs, one by ECT alone, and one by a combination of psychotherapy, drugs, and ECT. The average period of treatment was 24 days. Over two-thirds of the patients were committed by others. Three out of four patients showed significant symptomatic improvement while hospitalized, but only five remained well through a 6- to 15-month followup. Brief hospitalization seemed to provide a needed haven for the patients, but there was little change in their basic personality problems.

Washington University School of Medicine
St. Louis, Missouri

862 Wiener, Daniel N., Feinberg, Philip, Nagobads, I. J., Westendorf, F., & Warren, P. W. Effects of withdrawal of tranquilizers. Archives of General Psychiatry, 9:513-519, 1963.

The effects of chronic drug usage and withdrawal were studied in male outpatients (less than 65 years of age) who had been on tranquilizing drugs continuously for 18 months or more. Patients who were organically disabled or who were taking medication for a physical disability were not included. Random assignment placed 42 patients in a control group whose treatment regimen was not changed and 41 patients in a "withdrawn" group, from whom all drugs were to be eliminated. Patients in the latter group were rated and oriented to the study by medical investigators. All patients were rated by a therapist and took a personality test (MMPI). At the end of 3 months, ratings and tests were repeated. Of the withdrawn patients, 26 stayed off medication for the entire 3 months, 8 were never off medication, 5 stayed off drugs less than 1 month, and 2 dropped out during the study. There were no ill effects during the period of withdrawal. The degree of successful withdrawal was not related to the type of tranquilizer (phenothiazine or meprobamate) used. The partially withdrawn patients tended to show up as significantly worse on personality testing and ratings than did the completely withdrawn patients, thus demonstrating that the therapists' concern that withdrawal will arouse hostility is somewhat exaggerated. In general, there were no significant changes in type or intensity of problems and symptoms among the three groups during the course of the study, nor were there significant changes due to type of drug or to the diagnosis.

Veterans Administration Mental Hygiene Clinic
St. Paul, Minnesota

863 Aguilar, M. Toscano. La psilocybine: perspectives d'utilisation en psychiatrie clinique. (Psilocybin: Future prospects of its use in clinical psychiatry.) Acta Neurologica Psychiatricia Belgica, 63(2):114-131, 1963.

To make more precise the indications and contraindications of psilocybin, independent of clinical diagnosis, and to define a general psychotherapeutic technique, experience in the use of psilocybin with 35 hospitalized patients comprised of 27 males and 8 females (age and diagnosis not mentioned) is generalized. In small doses (0.5 mg/day), psilocybin may have strong psychotonic effect, which disappears after approximately 24 hours. The drug may be useful, at least when temporary "unblocking" of the patient is needed. Strong doses of 10 mg p.o. in the A.M. and in the P.M., attaining 16 mg, always produce somatic effects——most often that of diminution of pulse frequency, increase in arterial pressure, and increase in body temperature. Also, strong doses almost always produce psychic effects, which may be negative (decrease in affectivity, and absence of temporal perspective and of sense of direction) or positive (permanent euphoria in 14 of 16 cases, or else profound depression with suicidal ideas, plus hyperlucidity, depersonalization, and splitting of the psyche). The splitting of the psyche that is produced temporarily relaxes defenses, enabling the patient to

analyze the dynamic structure of his adaptive attitude. Valuable therapeutic results were obtained in behavioral difficulties (useful in diagnosis), in conditioned nonpsychopathic alcoholism, and in neurotic and reactionary depression. Excellent results were obtained in treating neuroses. (41 references)

(No address)

864 Tani, G. & Castellani, E. **Résultats cliniques et expérimentaux obtenus chez des sujets psychonévrotiques traités à la Dixyrazine. (Clinical and experimental results obtained with psychoneurotic subjects treated with dixyrazine.)** Acta Neurologica et Psychiatrica Belgica, 63:88-113, 1963.

Dixyrazine, a dichlorhydrate of 10-2-methyl-3-(1-hydroxyethyoxyethyl-4-piperazinyl) propyl phenothiazine, was tested on 100 patients (56 females and 44 males), aged 11 to 81 years (average age of 43 years), with duration of hospitalization from 8 to 31 days (average 16 days). The drug was given mostly in doses of 100 mg/day for adults and 40 mg/day for adolescents, and was reduced to 75 mg/day or increased to 250 mg/day, depending on patients' reactions and the side effects. The side effects found were minor sleepiness, some extrapyramidal symptoms, and slight difficulty in micturation, which disappeared when dosage was temporarily reduced. The patients were divided into two equal groups. The first group consisted of 27 females and 33 males, average age of 47 years, mostly aged patients and young patients with tics. The second group consisted of 29 females and 21 males, average age of 46 years, most patients being diagnosed as psychoneurotics. The second group was given the Pfister—Heiss color pyramid (Farbenpyramiden) test before and after drug. The results of the two groups show the drug has neuropsychiatric and nonneuropsychiatric therapeutic attributes. Neuropsychiatric effects are good general sedation, regulation of nervous insomnia, regulation of gastrointestinal and cardiovascular dystony, and anabolic action, particularly in asthenic subjects. Nonneuropsychiatric results are obtained in anxiety syndromes, particularly in anxiety psychoneuroses and psychogenic-depressive reactions. An attempt is made to explain the discrepancy between clinical results and the color-pyramid test results in the second group.

University of Ferrara
Italy

865 Madalena, J. C. **RO 4-8180——Nôve benzodiazepínico seu ensaio na neurose e na epilepsia. (Effects of RO 4-8180——A new benzodiazepine on neurosis and on epilepsy.)** Journal Brasileiro De Psiquiatria, 12(3):323-326, 1963.

In a preliminary therapeutic study, the tranquilizing and anticonvulsant effects of Ro-4-8180, a benzodiazepine derivative, were studied in two anxious neurotics and six chronic epileptics with generalized convulsions. Prior to the study, five of the epileptics had been taking 75 to 100 mg/day Ro-5-0690 (chlordiazepoxide) p.o., one had been taking chlordiazepoxide plus a combination of barbiturate and hydantoin, and the two neurotics had been taking 30 mg/day chlordiazepoxide p.o. After receiving 1 mg Ro-4-8180 t.i.d., p.o., one neurotic patient improved to the extent he could be considered cured. The other neurotic patient had to be shifted from the same dosage to chlordiazepoxide because of intolerance. In the five epileptic patients, the results produced by 3 mg/day Ro-4-8180 were inferior to those of chlordiazepoxide. The EEG of one neurotic and of one epileptic patient showed reinforcement of fast anterior rhythm, as is observed with chlordiazepoxide. Side effects included intense migraine, dysenteriform disturbances, and nausea. In the two epileptics, anxious depression was markedly greater than that observed with chlordiazepoxide. No side effects were noted in the two patients who had improved on the baribiturate—hydantoin combination. This experiment seems to indicate that Ro-4-8180 is inferior to chlordiazepoxide as an antiepileptic drug, and that it has more side effects.

Instituto de Psiquiatria
Universidade do Brasil

866 Madalena, J. Caruso. **As benzodiazepinas: Nova classe de substâncias anti-convulsivantes. Primeiras Comparacões. (Benzodiazepines. A new group of anticonvulsant drugs.)** Journal Brasileiro De Psiquiatria, 12(3):313-321, 1963.

In a comparative study of benzodiazepine derivatives, Ro-5-0690 (chlordiazepoxide), Ro-5-2807 (diazepam), and Ro-4-6006 were given to 10 chronic epileptic patients who had grand mal seizures. Therapy with barbiturates in combination with hydantoin had not been successful. The group included six females and four males, 25 to 55 years old; seven patients were hospitalized, and three patients were ambulatory patients. Each patient was given 75 to 200 mg chlordiazepoxide, 20 to 70 mg diazepam, and 2 to 6 mg Ro-4-6006 p.o., the interval between administra-

tions being determined by the occurrence of seizures. Hepatograms taken before and after administration of Ro-4-6006 showed no significant liver disturbance. Side effects with Ro-4-6006 included nausea and migraine in two cases, sleepiness in one case, and in one case, myoclonia of peribuccal muscles after 2 mg of the drug. The latter patient reported great improvement of dysmenorrhea. Based on the frequency of occurrence of seizures, the results were the following (> = "better attenuation of spacing of seizures, than"): Ro-5-0690 > Ro-4-6006 > Ro-5-2807 (5 cases); Ro-5-0690 > Ro-5-2807 > Ro-4-6006 (3 cases); Ro-4-6006 > Ro-5-0690 > Ro-5-2807 (1 case); and Ro-5-2807 > Ro-5-0690 > Ro-4-6006 (1 case).

Universidade do Brasil
Brazil, South America

867 Beyme, Von F. **Vergleichende therapeutische untersuchungen mit Valium (Roche) und Natriumbromid bei ambulanten Patienten mit neurasthenischem syndrom. (Comparative therapeutic investigations of valium (Roche) and sodium bromide in ambulatory patients with neurasthenic syndrome.)** Praxis, 52(45):1382-1387, 1963.

The effects of diazepam on 24 patients with neurasthenic syndrome were studied in a controlled clinical trial. The patients were divided into two groups: Group A consisted of 10 females and 2 males, 26 to 48 years old (average age, approximately 36), and Group B was comprised of 10 males and 2 females, 21 to 69 years old (average age, approximately 36). Group A received 10 mg diazepam p.o. for 1 week, which was followed by a placebo of 3.3% sodium bromide, 1 tsp at meals, for 1 week; Group B received the placebo first and then the drug. Of a list of 33 symptoms, Group A showed a total of 224 before the test. After 1 week on diazepam the number of symptoms dropped to 142 (-36%), but rose again to 174 (+22%) following 1 week on bromide. Group B began with a total of 212 symptoms, which dropped to 179 (-16%) after 1 week on sodium bromide, and dropped again to 135 (-24%) after 1 week on diazepam. Biometric examination, using five different statistical testing methods, showed probability values below 0.01 in all cases. The differences are highly significant, and diazepam can thus be recommended in the neurasthenic syndrome.

Steinengraben 79
Basel, Switzerland

868 Byme, F. **Erste Erfahrungen mit Valium (Roche) in der nervenärztlichen Privatpraxis. (Early experiences with valium (Roche) in neurological private practice.)** Praxis, 52(23):734-739, 1963.

A total of 20 neurasthenic patients (ages not mentioned) from private practice were treated with diazepam. Of a list of 32 symptoms, the 20 patients showed a combined incidence of 299. This dropped to 166 during diazepam treatment. The remission rate was very good in 3 cases, good in 11 cases, and insignificant in 6 cases. Very good improvement was obtained for individual symptoms of attacks of fear of death, feeling of suffocation, and nightmares; and good improvement was obtained with 24 other symptoms, including palpitation, dizziness, tremor, and insomnia. The best improvement was obtained usually within 1 week, and at most after 4 weeks. Therefore, in low dosage, diazepam has approximately the same effect on neurasthenic symptoms as chlordiazepoxide. Side effects were noted in eight patients——tired feeling in four, a narcotized feeling in two, dizziness in one, and confusion in one senile patient. These effects disappeared when dosage was reduced, and in the last two cases, when the drug was discontinued. Alcohol intolerance was observed in one 24-year-old anxious neurotic who had been on 10 mg/day for 11 days. Because effective daily doses compatible with unhindered professional activity lay between 1.25 and 30 mg, dosage should be determined individually for each patient. (25 references)

Steinengraben 79
Basel, Switzerland

869 Misès, R. & Beauchesne, H. **Essai de la perphénazine chez l'enfant et l'adolescent. (A test of perphenazine in infants and adolescents.)** Annales Médico Psychologiques, 2:89-92, 1963.

For approximately 4 months, perphenazine was administered to 29 children, 10 to 16 years old, t.i.d. in increasing doses (dosage not specified). The subjects were divided into four groups: (1) 4 cases of agitated semi-educable mentally defectives; (2) 6 cases of autoaggressive and heteroaggressive impulses in mentally deficients; (3) 15 cases of precocious psychoses with deficiency symptoms; and (4) 4 cases with psychotic evolution in puberty. In the majority of cases, the patients first received another neuroleptic, which gradually was replaced by perphenazine. The results were as follows: Group 1, marked improvement in 2, and effects equal to previously available drugs in 2; Group 2, ef-

fects superior to other drugs in 2 and equal to other drugs in 4; Group 3, marked improvement in 5, superior effects in 3, effects equal to other drugs in 5, and no effects in 2; Group 4, marked improvement in 1, superior effects in 2, and effects equal to other drugs in 1. No extrapyramidal symptoms were observed; sleepiness was noted in one case; clinical affection of liver, kidney, or blood was not observed; and the EEG readings that were taken showed no notable modification. A drop in epileptogenic threshold was noted in two girls with epileptic predisposition. Autoemetic action was observed in children showing vomiting of complex origin; hiatic hernia in one case leaves open the possibility of psychogenic factors.

(No address)

870 Lecomte, M. G. & Alcalay, R. **Essai de comparaison entre la trifluopérazine et les autres neuroleptiques dans le traitement des schizophrenies anciennes et des delires chroniques. (Comparative test of trifluoperazine and other neuroleptics in treatment of chronic schizophrenia and chronic delirium.)** Annales Médico-Psychologiques, 2:252-256, 1963.

The effects of trifluoperazine were compared with previous treatment that used other drugs. The group consisted of 47 patients, diagnosed as chronic schizophrenia or chronic delirium, 7 of whom were under 30 years old, 17 were between 30 and 50 years old, and 21 were over 50 years old. Duration of illness exceeded 5 years in 42 patients and 15 years in 33 patients. All drugs were suspended in 19 patients for 1 month prior to the study, and in another group of patients, 19 chemotherapy was switched abruptly to trifluoperazine. The previously used chemotherapy included chlorpromazine (25 patients), tementil (10), theralen (5), thioproperazine (4), levomepromazine (2), and thioridazine (1). Trifluoperazine was given p.o., in rapidly increasing doses, in combination with trihexyphenidyl or orphenedrine, plus Vitamins B_1 and B_6, attaining a maximum of 30 mg/day (15 mg/day for patients over 65 years old). Tolerance, on the whole, was satisfactory, and drowsiness was markedly less than with other neuroleptics. Seven patients became depressed while taking trifluoperazine. On the basis of five cardinal symptoms of chronic schizophrenia, the 47 patients showed a combined incidence of 142 symptoms. Trifluoperazine had a favorable effect on 101 symptoms. compared to 73 for previous neuroleptic therapy. The symptoms that improved were in contact with reality, impulsive reaction, inactivity, hallucinations, and delirium.

(No address)

871 Minvielle, J., Castan, Ph., Sportouch, Y., Arnaud, A., & Frayssinet, J. **Utilisation de la thioridiazine en clinique psychiatrique. A propos de 100 cas. (Clinical psychiatric use of thioridiazine in 100 cases.)** Annales Médico-Psychologiques, 2: 271-274, 1963.

The first 100 cases (64 hospitalized and 36 ambulatory patients) treated with thioridiazine in a psychiatric clinic were reviewed in a retrospective study. The group included 55 schizophrenics (42 hebephrenic and 13 paranoic), most with more than 5 years' illness, who had been subjected to various major therapies. Thioridiazine was administered in doses of 50 mg (liquid and tablet form), and post-treatment consisted of 10 and 50 mg/day p.o. Thioridiazine was used alone in 33 cases; in 67 cases, it was combined with insulin--pyretotherapy or anticomitics; and most often, it was accompanied by other neuroleptics (chlorpromazine, levomepromazine, R. 1625, alimemazine, thioproperazine, and prochlorpemazine). Tolerance was excellent on the whole. Some patients have been receiving 150 mg/day for more than 1 year with no annoying side effects. Drowsiness was seen in 25 patients who were receiving 150 mg/day or more. Therapeutic results were good in 17 cases, moderate in 59 cases, and no effect was noted in 20 cases. No aggravation of symptoms was observed. In the cases with moderate improvement or no effect, prochlorpemazine had better hallucinostatic effect than thioridiazine. Thioridiazine is a useful neuroleptic with good tolerance, producing no inconvenient side effects in doses of 150 mg/day or less.

(No address)

872 Naviau, J., Baré, Cl., & Duquesne, J. -P. **Essai de la perphénazine en thérapeutique psychiatrique. (Test of perphenazine in psychiatric therapy.)** Annales Médico Psychologiques, 2:98-104, 1963.

The effects of perphenazine were studied on 41 female hospitalized patients, 18 to 70 years old (average age, 38), in an experiment covering 12 months. The patients' diagnoses included: paraphrenia in 8, delirium and acute schizophrenia in 5, hebephrenia or hebephrenocatatony in 19, paranoic psychosis in 6, psychoneurosis in 2, and psychopathic personality in 1. All but two patients had

been treated previously with various neuroleptics. Dosage began with 12 mg perphenazine t.i.d., p.o. for 3 days, and was increased to 4 mg/day every 2 or 3 days; posttreatment was given when possible. Because of the almost constant occurrence of extrapyramidal side effects, most patients were given 10 to 15 mg/day trihexyphenidyle. Heptamynol was added for cardiovascular phenomena, and chlorpromazine was given when there was a tendency toward agitation. Effects were evaluated as complete remission (CR), incomplete remission (IR), improvement (I), no effect (NE), or worsening (W) of symptoms. The results showed: paraphrenic patients---2 CR, 1 IR, 4 NE, 1 W; delirious and acute schizophrenic patients---4 CR, 1 W; hebephrenic patients---4 CR, 4 IR, 2 I, 7 NE, 2 W; paranoic psychosis---1 I, 5 NE; psychoneuroses---1 CR, 1 I; and psychopathic personality---1 NE. Behavior later was normalized in the last named by levomepromazine. In cases reacting favorably, improvement appears at the end of 3 weeks to 1 month. With the exception of secondary extrapyramidal phenomena, general tolerance to the drug was good. Six patients had no extrapyramidal symptoms except for slight tremor. No correlation between the intensity of the neurological syndrome and therapeutic efficacy of the drug was noted.

(No address)

873 Ahbel, Andreas S. **Combination Rauwolfia-diuretic preparations in the treatment of hypertension.** Journal of the American Geriatrics Society, 11(7):673-678, 1963.

Flumethiazide and bendroflumethiazide (diuretic benzothiadiazine derivatives) were tested in combination with Rauwolfia for effect in treating hypertensive patients. Twenty-five patients, 17 women and 8 men, aged 39 to 83 years, were treated with tablets containing the following drug combinations: (1) 50 mg Rauwolfia and 400 mg flumethiazide plus potassium chloride; and (2) 50 mg Rauwolfia and 4 mg bendroflumethiazide plus potassium chloride. Dosage was one or two tablets daily. Fourteen patients received Rauwolfia-flumethiazide for an average of 4 months, and 11 received the other combination for an average of 7-$\frac{1}{2}$ months. Blood pressure was reduced in 11 of the 14 patients receiving Rauwolfia-flumethiazide from a mean of 155 to 132 mm Hg. Blood pressure was reduced in 8 of the 11 patients receiving Rauwolfia-bendroflumethiazide from a mean of 171 to 135 mm Hg. No serious side effects were reported. Lightheadedness and drowsiness were reported with Rauwolfia-flumethiazide. Lightheadedness was reported by three patients taking the other combination, and one patient complained of nausea, but no drowsiness was reported; treatment was discontinued in one patient because of persistent leg cramps. Both combinations were judged to be effective antihypertensive agents, especially in elderly ambulant patients with chronic fluid retention.

Mercy-Timken Mercy Hospitals
Canton, Ohio

874 Shubin, Harry & Glaskin, Allen. **Advantages of benzquinamide therapy for control of anxiety-depression in the elderly.** Journal of the American Geriatrics Society, 11(8):793-796, 1963.

Benzquinamide, reported to induce tranquilization without interfering with mental activity or physical coordination, was tested in 33 geriatric patients (64 to 80 years of age) and in 18 young and middle-aged patients (35 to 54 years of age) with anxiety-depression and personality disorders. Initial dosage was 25 mg q.i.d. in all but one patient. According to individual response, dosage was lowered to 25 mg t.i.d., and then to maintenance doses of 25 mg b.i.d. Average duration of therapy was 10 months. The response to benzquinamide was excellent in 15 patients, good in 29, fair in 4, and poor in 3. Therapeutic response was first observed from 12 to 96 hours after initial therapy in 34 cases, and from 96 hours to 1 week in 10 cases; in the remaining 7 cases, response was fair to poor. Nineteen patients complained of mild to moderate insomnia and/or nervousness (shakes), which disappeared on reduction of dosage.

6601 North 21st Street
Philadelphia 38, Pennsylvania

875 Stern, Francis H. **Comparison of three agents (Tigacol, Dramamine and Antivert) for the control of dizziness in geriatric patients.** Journal of the American Geriatrics Society, 11(9):884-890, 1963.

A double-blind study was made of the comparative effectiveness of nicotinyl alcohol (50 mg)-trimethobenzamide (100 mg), dimenhydrinate (50 mg), and meclizine dihydrochloride (12.5 mg)-nicotinic acid (50 mg) in controlling the vertigo-nausea-vomiting syndrome associated with vascular dysfunction in geriatric patients. The 27 female and 23 male patients ranged in age from 47 to 88 years. A major symptom in all cases was dizziness associated with varying degrees of nausea and vomiting, which had been present

from 6 months to 15 years. In 41 cases the diagnosis was cerebral arteriosclerosis, in 5 cases Ménière's disease, in 3 cases multiple sclerosis, and in 1 case vertigo caused by an acoustic neuroma. All antivertigo-antiemetic medication was discontinued for 1 week; then all patients received a placebo for 1 week. Each active drug was given for a 3-week period with 1-week intervals of no medication. The initial dosage of each drug was 1 capsule t.i.d. When response was minimal, this was increased to 1 capsule q.i.d. With dimenhydrinate, there were no excellent results and only 11 good results; with trimethobenzamide-nicotinyl alcohol, there were good to excellent results in 43 patients; and with meclizine-nicotinic acid, there were good to excellent results in 38 patients. Side effects occurred least often with trimethobenzamide-nicotinyl alcohol. Except for drowsiness during dimenhydrinate therapy, side effects were typical of those caused by nicotinic acid derivatives. In no case did side effects necessitate discontinuance of therapy.

332 South 21st Street
Philadelphia, Pennsylvania

876 Feinblatt, Theodore M. & Ferguson, Edgar A., Jr. **Sedative and somnifacient effects of methapyrilene-niacinate: Comparison with methapyrilene hydrochloride in 53 cases.** Journal of the American Geriatrics Society, 11(9):909-913, 1963.

A double-blind comparison of methapyrilene-niacinate with methapyrilene hydrochloride was carried out in 53 patients whose main complaint was insomnia. Additional diagnoses included bronchial asthma, obesity, menopausal syndrome, anxiety state, hypertension, tachycardia, colitis, and diabetes mellitus. The study group included 30 females and 23 males (average age of 48 years). The duration of insomnia averaged 4 years; periods of treatment and observation ranged from 3.3 weeks to 5.9 weeks. The types of insomnia were classified into four groups: early evening insomnia (23 cases), nocturnal restlessness (19), early morning wakefulness (9), and insomnia associated with bronchial asthma (2). In all cases, the dosage was 50 mg, calculated as methapyrilene base, taken at bedtime. Methapyrilene-niacinate was 46% more effective than methapyrilene hydrochloride with respect to the number of hours of sleep gained in all four types of insomnia. There were no serious side effects with methapyrilene-niacinate. Mild anorexia occurred in two cases and an erythematous rash in one case. Toxicity studies in animals indicate a wide margin of safety for the drug combination.

150 Woodruff Avenue
Brooklyn, New York

877 Stern, Francis H. **Value of carisoprodol (Soma) in relieving leg cramps.** Journal of the American Geriatrics Society, 11(10):1008-1013, 1963.

A double-blind, crossover, placebo-controlled design was used to determine the effectiveness of carisoprodol, a muscle relaxant with analgesic action, in treating 50 geriatric patients with intermittent claudication or nocturnal leg pains. The 50 patients were divided into two groups, each having 8 men and 17 women; the average age for group I was 67 years and for group II was 66 years. For the first four weeks of the trial, group I received carisoprodol and group II received the placebo. Drugs were then discontinued for 1 week. After this, group I took placebo and group II took carisoprodol. All patients received one tablet of carisoprodol or placebo q.i.d.; carisoprodol tablets contained 350 mg of the drug. Dosage was increased to six tablets daily in some cases. Seventeen patients in each group received concomitant medications, such as barbiturates, digitalis, protein supplements, and diuretics. In 41 (82%) of the 50 patients, response to carisoprodol was excellent or good. Only one patient showed a good response to placebo. Seventeen patients complained of drowsiness. Of the 17 patients, 2 also complained of mental confusion, 1 of nausea, 1 of headache, and 1 of epigastric pain. Five other patients reported pruritus of the hands, pruritus of the ani, tingling around the mouth, mild headaches, and glossitis, but these symptoms may have been related to other factors.

332 South 21st Street
Philadelphia 3, Pennsylvania

878 Chesrow, Eugene J., Kaplitz, Sherman E., Breme, John T., & Vetra, Helga. **Use of carisoprodol (Soma) for treatment of leg cramps associated with vascular, neurologic or arthritic disease.** Journal of the American Geriatrics Society, 11(10):1014-1016, 1963.

A clinical trial of carisoprodol was conducted among 24 male and 21 female patients (median age, 52.9 years) with various neurologic, vascular, or arthritic diseases. The predominant complaint was leg cramps, characterized by pain, muscle spasm, spasticity, or tenderness. Either drug (350 mg q.i.d.) or placebo, in identical tablets, was adminis-

tered over a 10-week period. There was definite improvement in 21 of 26 patients receiving carisoprodol; in 5 patients, the improvement was minimal. In 19 patients treated with placebo, the maximal result was slight relief of leg cramps in 5 cases. In a second trial, 24 patients received carisoprodol for 6 weeks. Of these patients, 19 had previously received placebo and 5 had been previously treated with other drugs. In 14 of the 24 patients, there was complete or marked relief of leg pain, muscle spasm, and tenderness; in 7, there was slight relief; and in 3, there was no relief. Mild and transient side effects were noted in six patients, primarily during the first or second week of the study.

Oak Forest Hospital
Oak Forest, Illinois

879 Marsh, D. O., Schnieden, H., & Marshall, John. **A controlled clinical trial of alpha methyl dopa in parkinsonian tremor.** Journal of Neurology, Neurosurgery and Psychiatry, 26(6):505-510, 1963.

The effects of an acute dose of α-methyldopa were studied by observing patients clinically, by recording their tremors graphically, and by a double-blind trial. Ten patients were given an acute oral dose of 2 g of α-methyldopa; three of these had their usual antiparkinsonism drugs withdrawn. In all but one case, the effect of the drug in reducing the amplitude of tremor was greater than that of the placebo. Five men and five women (ages 44 to 70 years) participated in the double-blind trial; five of these were severely affected by parkinsonism, two were moderately affected, and three were mildly affected. The trial was conducted over four 1-week periods. During each period, the patient was given 1.0 or 1.5 g of either α-methyldopa or placebo in a random order. Each patient continued to take his previous medication, which included benzhexol, orphenadrine, benztropine, and ethoheptazine. Doses of 1 to 1.5 g/day for 1 week were effective in diminishing tremor in the majority of the patients. The effect on blood pressure was negligible at this dose, but sedation (5), depression (3), faintness (2), dry mouth (2), and diminution in bowel frequency (1) were reported

National Hospital of Nervous Diseases
London, England

880 Rodová, A., Náhunek, K., Bártová, D., & Továrek, J. **Klinické zkušenosti s thioxanthenovým derivátem. (Clinical experience with Sordinol, a derivative of thioxanthene.)** Activitas Nervosa Superior, 5:197, 1963.

Clinical experience with chlorpenthixol was derived from treatment of 27 patients, 16 to 67 years old, including 22 females and 5 males. Maximum dosage was 125 mg/day i.p. and 375 mg/day p.o. The course of therapy covered 7 to 29 days. Favorable results were obtained with 5 of the 10 schizophrenics (3 of those improved had paranoic hallucinatory syndrome). Of four manic syndromes, two were calmed by chlorpenthixol i.p. One patient with chronic obsessive neurosis was unimproved. In this respect, it must be noted that due to an insufficient supply of the preparation, higher doses could not be tested. When chlorpenthixol was replaced by 48 to 72 mg/day perphenazine, improvement was similar to that obtained with chlorpenthixol. Perphenazine produced remission in one of the five patients unimproved by chlorpenthixol. Of 12 endogenous depressive patients treated with a combination of chlorpenthixol and Triphenidyl (6 mg/day), favorable therapeutic results were obtained in three, indicating weak antidepressive action of the drug combination. Medication parkinsonism was observed in 9 of 15 patients treated exclusively with chlorpenthixol, and two patients showed excitomotor crises of facial musculature. Other side effects included weakness, fatigue, drowsiness, headache, tachycardia, and drying of mucus membranes. The combination of chlorpenthixol and Triphenidyl was found to be less effective than the analogous combination of perphenazine and Triphenidyl.

Brno, Czechoslovakia

881 De Sousa E Almeida, Waldir. **Avaliaco clinica do dicloridrato de flufenazine. (Clinical evaluation of fluphenazine dihydrochloride.)** Arquivos Neuropsiquiatria, 21:35-38, 1963.

A preliminary clinical evaluation of fluphenazine was done on 12 chronic psychotics, including 8 white and 4 Negro patients, 27 to 63 years old. The subjects had had various previous psychiatric treatments, and some had been lobotomized. The duration of illness ranged from 8 to 26 years, with the majority in the 10- to 17-year range (8 cases). Diagnoses included 1 hebephrenic schizophrenic, 5 catatonic schizophrenics, 1 hebephrenic-catatonic schizophrenic, 3 paranoic schizophrenics, 1 hebephrenic-paranoic schizophrenic,

and 1 oligophrenic patient. The initial injected dose of 5 mg/day fluphenazine was increased by 5 mg/day until extrapyramidal symptoms appeared. The doses varied between 35 and 90 mg/day. Parkinsonism occurred in one patient at 10 mg/day, yet 240 mg/day failed to produce symptoms in one Negro patient. The criteria used for the evaluation of drug effects included the occurrence of nocturnal unrest, authoritarian attitude, and hostility. In general, patients with these manifestations benefited more from the drug than the passive, withdrawn patients. Side effects included diarrhea in two patients, and hypothermia lasting several days in three patients. Best results were obtained with the paranoic-schizophrenic patients. No correspondence between dosage and clinical improvement was observed. Fluphenazine may be considered a useful psychiatric therapeutic for long-term treatment.

Jacarepaguá, Rio de Janeiro
Brazil

882 Cass, Leo J. & Frederik, Willem S. **Methopholine, a new analgesic agent.** American Journal of Medical Sciences, 246(5): 550-557, 1963.

The relative analgesic effectiveness of a combination of methopholine with aspirin--phenacetin--caffeine (APC) and of methopholine alone, in relation to other analgesic compounds (APC and codeine--APC) and also in relation to placebo, was studied in 34 patients with chronic pain due to various causes. Among the 27 males and 7 females (average age of 57.1 years) who completed the double-blind study, initial pain severity was severe in 5 instances, moderate in 18, and mild in 11. The subjects, who served as their own controls, received each of the medications in a random sequence for a 6-day period, followed by a drug-free day before they were rotated to the next drug. Medications were given 4 times a day, and observations on degree of pain relief were made, by means of a sliding scale, 90 minutes after each of the first three daily administrations. The resulting data were subjected to statistical analysis which showed the following: (1) All four analgesic medications were significantly better than the placebo. (2) The differences between the efficacy of methopholine (plain) and APC (plain) and of methopholine--APC and codeine--APC were not significant. (3) Both methopholine--APC and codeine--APC were significantly better than either methopholine (plain) or APC (plain).

Harvard University
Cambridge, Massachusetts

883 Lindeman, Robert D., Bouthilet, George N., Ashley, Wayne R., & Morris, John R. **Effect of hydrochlorothiazide-reserpine therapy on cerebral function in elderly hypertensive patients.** Journal of the American Geriatrics Society, 11(6):597-606, 1963.

This study was made to determine whether or not elderly hypertensive subjects can tolerate a substantial reduction in blood pressure for a prolonged period (5 to 6 weeks) without changes in cerebral function. Antihypertensive agents or identical-appearing placebos were administered; a series of seven psychologic tests, recognized to be sensitive indicators of changes in intellectual efficiency, the Clyde Mood Scale, and EEG's were given before and after the medications. The subjects were screened from 2,000 patients--- those chosen were over 60 years of age with a systolic blood pressure above 160 mm Hg or a diastolic pressure above 100 mm Hg that remained above these levels. A group of 36 patients, 18 male and 18 female, received p.o. either 50 mg hydrochlorothiazide t.i.d. for 1 week, followed by 0.25 mg reserpine t.i.d. in addition for 5 to 6 weeks (14 patients), only reserpine (5 patients), or placebo (17 patients). In 14 patients, hydrochlorothiazide and reserpine produced a mean drop of blood pressure amounting to 50.6 mm Hg systolic and 21.0 mm Hg diastolic. In 17 patients on placebo, the mean drop was 23.8 mm Hg systolic and 8.6 mm Hg diastolic. In five patients given reserpine alone, the drop in pressure was similar to the placebo group. The only side effects were postural dizziness in two combination-drug patients and rhinitis in one reserpine-alone patient. Psychologic tests and EEG's obtained before and after treatment indicated that these elderly patients could tolerate significant drops in blood pressure for this length of time without demonstrable changes in cerebral functioning.

Oklahoma Medical Center
Oklahoma City, Oklahoma

884 Foldes, Francis, F., Lunn, John N., Moore, James, & Brown, Ian M. **N-allylnoroxymorphone: A new potent narcotic antagonist.** American Journal of Medical Sciences, 1(1):23-30, 1963.

Five μg/kg N-allyl oxymorphone administered intravenously to a group of 10 lightly anesthetized subjects, who were not premedicated by narcotics, caused no significant respiratory or circulatory changes. However, it prevented, to a considerable extent, the respiratory depressant effects of 20μg/kg oxymorphone administered 5 minutes later. In

the other three groups of 10 patients each, premedicated with meperidine and lightly anesthetized with thiopental and nitrous oxide-oxygen, 5μg/kg N-allyl oxymorphone effectively antagonized the severe respiratory depression caused by 20μg/kg oxymorphone, 2.0 mg/kg meperidine, or 0.66 me/kg alphaprodine, respectively. Five μg/kg N-allyl oxymorphone, administered 5 minutes before, did not prevent the circulatory effects of 20μg/kg oxymorphone. When administered 7 minutes after oxymorphone, N-allyl oxymorphone partially antagonized the circulatory effects of the former. On an mg/mg or molar basis, N-allyl oxymorphone is 6 times and 30 times more effective in antagonizing narcotic-induced respiratory depression than levallorphan or nalorphine, respectively. (Author abstract, edited)

Mercy Hospital
Pittsburgh, Pennsylvania

885 Shelburne, Palmer F. & Orgain, Edward S. **Comparison of syrosingopine and reserpine in the treatment of ambulatory hypertensive patients.** American Journal of Medical Sciences, 1(3):304-310, 1963.

Twenty-one outpatients (average age of 54 years) exhibiting mild or moderate hypertension had no significant change in blood pressure after 3 or more weeks' therapy with syrosingopine (4 mg p.o. daily). The same patients had modest, but consistent, reductions in blood pressure (average fall of mean blood pressure 10 mm Hg recumbent and 11 mm Hg standing) on 1 mg reserpine daily. In only one patient on syrosingopine and in only 3 patients on reserpine was the mean recumbent blood pressure lowered as much as 20 mm Hg. Mild symptoms of nasal stuffiness, gastrointestinal distress, insomnia, or nightmares occurred nearly twice as often in the patients during administration of reserpine.

Duke University Medical Center
Durham, North Carolina

886 Borenstein, P., Bles, G., Dabbah, M., & Croize, B. **Un nouveau correcteur des syndromes extra-pyramidaux induits par les neuroleptiques: l'éthybenzatropine (UK 738). (Ethybenzatropine (UK 738), a new corrector of extrapyramidal syndrome induced by neuroleptics.)** Psychiatria et Neurologia, 745: 144-179, 1963.

Tropethydryline was clinically tested on 96 patients, including 77 patients under neuroleptic therapy, in 115 courses of treatment, totaling 3,700 treatment days. In addition, EEG studies were made in 84 cases. Tropethydryline, given parenterally (4 to 8 mg i.v. or 5 to 15 mg i.m. daily) and then orally (15 to 30 mg/day), controlled both the early paroxysmal excitotonic states (in all cases) and Parkinson-like symptoms (in approximately 90% of cases). This double therapeutic effectiveness is a unique feature of the drug. Its action on parkinsonian symptoms and chorea is, on the whole, equal to classic compounds, such as trihexyphenidyl, and is occasionally superior; the action sometimes differs from that of trihexyphenidyl in regard to individual symptoms. Tropethydryline complements neuroleptics both in control of anxiety and in elimination of psychomotor inhibition. The somatic side effects are not constant, but generally are moderate and readily tolerated, most often resembling those of atropine. Side effects necessitated suspension of treatment in fewer than 3.5% of the cases. Local tolerance was excellent in i.v., i.m., and p.o. administration. Tropethydryline appeared to "activate" the EEG of epileptics in approximately half the cases, although it caused no clinical aggravation in 15 patients subject to comas. Tropethydryline is considered to be a particularly effective and an easily managed "corrector" of extrapyramidal symptoms, enabling the use of new neuroleptics with patients previously unable to take neuroleptics because of annoying side effects. (25 references)

Hôpital Psychiatrique de Villejuif
Seine, France

887 Aresin, Lykke. **Therapeutische Möglichkeiten bei der Anwendung won Trioxazin. Einem neuen Tagessedativum. (Therapeutic possibilities in the application of trioxazin. A new daily sedative.)** Zeitschrift Aerztlichen Fortbilding, 57:111-114, 1963.

Trioxazin, a trimethoxyphenyl derivative, was tested on 65 clinical patients, 50 females (19 to 53 years of age) and 15 males (23 to 44 years of age). The drug was available only in 300-mg tablets. After 2 or 3 days on 1 tablet morning and night, dosage was gradually increased to as much as 4 tablets b.i.d. (1,800 mg/day) in some climacteric patients. The optimal dosage was maintained for 3 to 6 weeks, and then was gradually reduced. When the morning dose was withdrawn, many females reported improvement of insomnia.

Anxiety-depression syndrome disappeared in 3 to 4 weeks in 21 female patients. The drug had favorable effect on vegetative and vasomotor symptoms of 18 climacteric patients. Results were not so markedly favorable in five carcinophobic hypochondriacs, and results were inconclusive in two paranoic schizophrenics, two cyclothymic cases, and two postoperative psychoses. Small doses (1/2 to 1 tablet t.i.d.) produced complete remission of psychogenic ejaculatio praecox and occasional impotence in 12 of the 15 males within 5 to 8 weeks. Trioxazin is a new minor tranquilizer with very good tolerance and minimal toxicity. It is well suited as a daily sedative, and appears to be specifically indicated for relieving potency disturbances by virtue of its tension-relieving effect.

Gynecological Clinic
Karl Marx Universität
Leipzig, Germany

888 Vass, P., Bornemisza, J., & Hadnagy, Cs. **Die Wirkung von Reserpin auf den Kohlenhydratstoffwechsel bei Diabetes. (Effect of reserpine on carbohydrate metabolism in diabetics.)** Für Verdauungs- Und Stoffwechselkrankheiten, 22(5-6):263-266, 1962.

The effects of Rauwolfia serpentina on carbohydrate metabolism were tested in 92 static diabetic patients (25 to 80 years old, 30% males and 70% females). The reserpine effect was assayed in 56 patients by determination of daily blood-sugar level. In 19 of the 56 patients, blood-sugar level fell an average of 25%. In 4 patients, carbohydrate metabolism worsened markedly, and 33 patients showed no substantial change. The reserpine effect was tested in 30 patients by control of glucose tolerance. Results showed that carbohydrate metabolism substantially improved in 5 cases; improvement was slight in 1 case; there was no substantial change in 13 cases; and worsening was observed in 3 cases. Rauwolfia therapy produced no substantial change in a test of insulin sensitivity in 6 patients. All cases of good effect of reserpine on carbohydrate metabolism consisted of diabetics who had not been subjected to any antidiabetic medication, who had mild cases of diabetes, or who reacted well to hypoglycemia-producing sulfonamide. A very favorable therapeutic effect was observed in all patients for whom insulin is indicated, and in whom the disease was aggravated by hyperthyreosis. All cases in which reserpine had unfavorable effect on carbohydrate metabolism were also diabetics under insulin treatment. The authors suggest that Rauwolfia serpentina preparation be given to hypertonic diabetics only with strict control of blood sugar because of the danger of acetonuria complication.

Polyclinics Nos. I and II
Lupeni Hospital, Rumania

889 Mariategul, Javier, Del Villar, E. Ramirez, Otarola, P., & Bachmann, C. **El glucagon en la interrupcion del coma insulinico. (Glucagon in interruption of insulin coma.)** La Revista De Neuro-Psiquiatria, 15(4): 384-394, 1962.

Glucagon hydrochloride (HGF) was used in a pilot experiment to interrupt insulin coma in 18 male schizophrenics (13 paranoic, 2 catatonic, 1 hebephrenic, and 2 catatonic-paranoic) aged 17 to 44 years. The patients included 2 acute cases and 16 chronic cases of varying duration. The classic method of Sakel was used in insulin treatment. The patients received 50 to 180 units of insulin, with an average of 115 units. Glucagon was administered i.m. in 1-mg doses. A total of 152 interruptions was obtained, (18 in one patient, 11 in two patients, 10 in two patients, 9 in four patients, 8 in six patients, 6 in one patient, and 1 each in two patients. Of these 152 interruptions, 151 or 99.3% were arousals. No arousal was observed in one patient who had, however, previously interrupted with glucagon. The average recuperation time of the group was 15.1 minutes, with 126 cases (82.8%) recuperating in 10 to 20 minutes. Two patients who had received precoma EST responded satisfactorily to glucagon on two occasions, without notable change in recuperation time. During the course of treatment, no retardation in appearance of coma was noted, nor was it necessary to vary the number of insulin units to produce coma. The authors beleve that glucagon i.m. is useful in psychiatric insulin therapy. It has the advantages of applicability to a large number of patients, it may be used with belligerent patients, and it avoids i.v. injection in patients with sclerotic tendencies. (27 references)

(No address)

890 Dohan, F. Curtis, Durkin, John, Kulick, Alan, Rosenblum, Marcus P., Bachrach, David L., Grasberger, Joseph, Lynch, Frank B., Jr., & Sprince, Herbert. **Ineffective neomycin therapy of schizophrenia---Observations on urinary indoles.** Archives of General Psychiatry, 9:520-523, 1963.

Seven male patients (ages 28 to 37 years) with an increase in symptoms of schizophrenia within 1 to 3 months prior to rehospitalization were chosen for study. All had been hospitalized for an initial schizophrenic episode from 5 to 17 years prior to the study, and had been rehospitalized one to four or more times. None of the patients had any other disease requiring treatment or study. Four other patients (ages 37 to 44 years), diagnosed as "schizophrenic reaction," who had been in the hospital for 9 to 16 years, were also studied. Psychiatric ratings were made at 2-week intervals, using the Brief Psychiatric Rating Scale devised by Overall and Gorham. The dose of neomycin was 0.5 g q.i.d. or 1.0 g q.i.d. In the later periods, phthalylsulfathiazole 1.0 g q.i.d. was given with the neomycin. The seven relapsed and four chronic patients were studied as pairs (with one exception) selected for similarity of symptoms. After an initial 2 weeks of antibiotic or placebo therapy, all patients had 2 to 12 weeks of continuous antibiotic administration; the chronic patients also received their usual dose of chlorpromazine. Free and total indoleacetic acid was measured in urine samples by the method of Weissboch, et al. There was no evidence of improvement attributable to oral antibiotic therapy in any of the relapsed or chronic schizophrenic patients. Antibiotic intake resulted in the disappearance of 6-hydroxyskatole from the urine extracts, but had little effect on the urinary excretion of indoleacetic acid.

University of Pennsylvania
School of Medicine
Philadelphia, Pennsylvania

891 Poirier, Louis J., Richer, Claude L., Berthiaume, Marcel, Gravel, Gaston, Beaulines, Rita, & Martel, Pierre. **Adrenocortical and autonomic reactivity in schizophrenia.** Archives of General Psychiatry, 8:605-613, 1963.

More than 300 patients of both sexes (ages 40 to 50 years), mostly chronic schizophrenics who had been in a mental institution for a number of years, were the subjects in a study of peripheral reactivity. Various curves based on hematological cell counts, on glucose and hydrocortisone, determined from blood samples collected during a 4-hour period of fasting, and on the blood pressure recorded concomitantly to the latter data during 20 minutes were used to measure the degree of reactivity of the patients under various conditions. The estimate used to test reactivity included i.m. injection of isotonic saline (2 cc) or methacholine (8.3 mg/2 cc) and the i.v. injection of epinephrine (0.25 mg). Chlorpromazine (50 to 200 mg daily) and prochlorperazine (15 to 45 mg daily) were given orally during a period of at least 2 weeks prior to each test. In most cases, all data were recorded 2, 3, or 4 times in the same patient under various conditions. Most patients reacted to the injected saline by a small and gradual drop in blood pressure, to methacholine by an immediate and marked drop of blood pressure that was somewhat depressed after treatment with tranquilizers, and to epinephrine by a rapid rise of blood pressure that did not change after treatment with tranquilizers. Blood-cell counts revealed the absence of any consistent lymphopenic and eosinopenic reaction in response to isotonic saline and methacholine. Epinephrine injection was followed by a significant drop of eosinophils only after treatment with tranquilizers. Plasma hydracortisone determination revealed no signs of adrenal hyperactivity.

Université de Montréal
Montréal, Canada

892 McFarland, H. Richard. **Chlordiazepoxide for spasticity.** Diseases of the Nervous System, 24(5):296-298, 1963.

A preliminary open study of chlordiazepoxide on 35 patients with spasticity produced encouraging results. Subsequently, a double-blind study was done on 30 patients with objective signs of spasticity, whose ages ranged from 12 to 75 years. Each patient received 10 mg q.i.d., p.o. for 3 days of drug or of placebo; this was followed by an immediate crossover. Patients were examined for objective changes and were asked for subjective opinions. Of the patients in the open study, 68% received both objective and subjective improvement. In the double-blind study, chlordiazepoxide was more effective in 21 cases, and placebo was more effective in 9 cases. Drug effectiveness did not seem related to age, sex, diagnosis, or degree of spasticity. Improvements included ability to bend previously rigid limbs, amelioration of painful extremity spasms, disappearance of spontaneous clonus, relief from painful bladder spasms, improvement of cerebral palsy, and increased locomotion in incapacitating athetosis. Side effects were sought in the open study. Eleven patients had complaints; three complaints occurred at the usual dose of 40 mg/day or lower. Of 12 patients receiving more than 40 mg/day, 8 showed side effects, including fatigue in five, weakness of affected limbs in three, ankle edema in two, and headache and increased dyspnea each in one patient.

University of Michigan
Ann Arbor, Michigan

893 Mariuz, Mario J. & Walters, C. J. **Enuresis in non-psychotic boys treated with imipramine.** American Journal of Psychiatry, 120:597-599, 1963.

Imipramine in 25 mg p.o. daily doses was tested in 23 severely enuretic boys, aged 5 to 11, and weighing 52 to 100 pounds, to ascertain the drug's ability to control enuresis. The study was divided into two parts. Part I, a double-blind trial, consisted of three 20-day periods---(1) initial observation with no medication; (2) 11 boys receiving imipramine and 12 receiving placebo; and (3) imipramine and placebo dosage reversed. Part II, immediately following the double-blind test, was an open clinical trial with two 10-day periods---(1) no medication; and (2) all 23 boys receiving 25 mg imipramine. In Part I, 17 of 23 boys showed marked improvement on the drug, when compared with placebo. Nightly incidence of enuresis was reduced from a mean of 70% to 47%. In Part II, during the 10 days without medication, enuresis (63.5%) reverted to near the pretreatment level. In the following 10 days on imipramine, enuretic episodes decreased to 36.5%. No side effects were noted at the doses of imipramine used.

St. Agnes School
Sparkill, New York

894 Dorfman, Wilfred. **The use of protryptyline (MK-240) as an anti-depressant. A preliminary report.** American Journal of Psychiatry, 120:594-595, 1963.

Protryptyline, a derivative of amitriptyline that produces less drowsiness than the parent drug, was tested in 61 patients with various types of depression. Dosage was 15 to 30 mg/day. Of the patients tested, protryptyline was effective in 29 and was ineffective in 24; 8 patients did not return for further study after being placed on the drug and, therefore, could not be evaluated. Protryptyline was most effective in patients with retardation and apathy (without agitation). Patients with marked agitation did poorly; in some patients, agitation emerged as the depression lifted. The drug showed some promise in depressed psychoneurotics with obsessive-compulsive defenses.

1921 Newkirk Avenue
Brooklyn, New York

895 Zrull, Joel P., Westman, Jack C., Arthur, Bettie, & Bell, William A. **A comparison of chlordiazepoxide, d-amphetamine, and placebo in the treatment of the hyperkinetic syndrome in children.** American Journal of Psychiatry, 120:590-591, 1963.

The effectiveness of chlordiazepoxide in controlling the hyperkinetic syndrome in children was compared with that of d-amphetamine and placebo. Fifteen boys and one girl, aged 7 to 14 years, with I.Q.'s ranging from 65 to 118 (mean of 98), were tested. The d-amphetamine was given in doses of 5 mg b.i.d., and chlordiazepoxide was given in doses of 10 mg b.i.d. A double-blind, crossover pattern was used in administering the drugs. Prior to the 8-week drug treatment, the children were given a variety of psychiatric and psychological tests, a reading test, and a medical examination. On the third and sixth visits, interim examinations were made. On the last visit, tests administered prior to treatment were given again. The d-amphetamine was more effective than chlordiazepoxide in reducing the signs of hyperkinetic syndrome, and both chlordiazepoxide and d-amphetamine were more effective than placebo.

University of Michigan
Ann Arbor, Michigan

896 Brill, Joseph M. **Treatment of the acute alcoholic with injectable thioridazine.** American Journal of Psychiatry, 120:496-497, 1963.

Thioridazine was tested in 41 alcoholic patients, 30 male and 11 female, aged 33 to 65 years, for effect in symptomatic treatment of acute alcoholism. Each patient received 25 mg thioridazine hydrochloride by deep intragluteal injection every 4 hours for 5 days. Improvement was noted 4 to 6 hours after the first injection. Marked reduction of tension or anxiety and alleviation of depression were obtained within 24 hours in 26 patients; these improvements in the remaining patients were noted within 72 hours. Patients had a marked increase in appetite and became alert and cooperative. Blood-pressure recordings showed a mean fall of 10 mm Hg systolic and 5 mm Hg diastolic over a 5-day period. The only side effect was a 20 to 30 mm Hg fall in systolic blood pressure in three patients, which was relieved by a reduction in the frequency of injections. Thioridazine did not induce extrapyramidal stimulation or hepatotoxicity in any of the patients.

Wawa Hospital
Wawa, Pennsylvania

897 Karacan, Ismet, Jones, Frank, & Ersevim, Ismail. **Evaluation of combined antidepressant and tranquilizing drug (amitriptyline-perphenazine) in the treatment of hospitalized chronic schizophrenic patients.** American Journal of Psychiatry, 120:500-501, 1963.

The therapeutic effect of combined amitriptyline--perphenazine was determined in 19 female chronic schizophrenic patients, ranging in age from 20 to 60 years (mean, 42 years) who had been hospitalized 2 to 15 years (mean, 7 years). The patients had been receiving tranquilizers for a number of years, and all had received ECT. The combination tablet contained 25 mg amitriptyline and 4 mg perphenazine. The initial dose of 2 tablets was increased weekly until the end of the fourth week, and a dosage of 6 tablets/day was maintained for 8 weeks. Patients were evaluated initially and during the study in terms of standard rating scales, ward behavior and global clinical judgment. Of the 19 patients, 3 showed marked improvement, 2 showed moderate improvement, and 11 showed slight behavior improvement; 1 showed no improvement, and the drug was withdrawn from 2. Blood pressure showed minor changes during treatment. One patient developed Parkinson's syndrome. Observations and test data indicate that the patients showed improvement on the drug combination, but since there was no placebo control, no definite conclusions could be drawn.

Rhode Island Medical Center
Howard, Rhode Island

898 Krakowski, Adam J. **Treatment of severe depression with desipramine, a metabolite of imipramine.** American Journal of Psychiatry, 120:494-496, 1963.

Desipramine, an active metabolite of imipramine, was tested in 129 patients---35 males and 94 females aged 18 to 78 years---with severe depressive disorders. The majority had a history of 1 to 4 depressive attacks. In most cases, the drug was given for 2 to 4 months in daily doses of 75 or 100 mg i.m. for a few days, and was followed thereafter by 100 to 150 mg/day orally. Tranquilizers were given concurrently as required in order to control agitation, anxiety, or insomnia. Despiramine produced a satisfactory clinical response in 99 (76.4%) patients. Compared to imipramine, the new drug seems to be slightly more potent on a dose-size basis; it has a faster onset of action, evident in 2 to 7 days; and side effects appear to be milder and of shorter duration. The most frequent side effects were dry mouth, perspiration, and constipation. In 10 patients, desipramine was withdrawn, but the side effect could not always be attributed to the drug. Because of its rapid onset of action and mild side effects, the drug was judged to be useful in treating severe depressive conditions.

Champlain Valley and Physicians Hospitals
Plattsburgh, New York

899 Oltman, Jane E. & Friedman, Sammuel. **Pargyline in the treatment of depressive illness.** American Journal of Psychiatry, 120:493-494, 1963.

Pargyline, a nonhydrazine MAO inhibitor, was tested in female patients with various depressive states. Patients were assigned at random to treatment with placebo (16 patients) or pargyline (35 patients) in the double-blind study. Pargyline was initiated in a dosage of 25 mg b.i.d. or t.i.d. and increased, as necessary, to a maximum of 50 mg t.i.d. Of the 35 patients on pargyline, 22 showed definite improvement; only 3 of 13 on placebo improved. The overall results with pargyline were satisfactory, but less so than those previously obtained with imipramine. Improvement under pargyline was manifested within 10 to 14 days. Side effects were chiefly the result of hypotensive phenomena: dizziness, fainting, and lightheadedness. These occurred at dosages of 150 mg daily, and were more prominent in middle-aged or elderly patients. Other side effects included slight edema of ankles (5 patients), drowsiness (1), mild perspiration (1), constipation (1), and urinary frequency or urgency (2).

Newtown, Connecticut

900 Gallant, D. M., Bishop, M. P., Timmons, E., & Steele, C. A. **Trifluperidol: A butyrophenone derivative.** American Journal of Psychiatry, 120:485-487, 1963.

Under double-blind conditions, the effects of trifluperidol, a butyrophenone derivative, were compared with the effects of chlorpromazine in each of two groups of 18 chronic schizophrenics who had received no medications for at least 60 days. The period of study was 10 weeks, with the maximum dosage of trifluperidol (6 mg/day) and of chlorpromazine (1,200 mg/day) being attained at the beginning of the fifth week. Psychologic and psychiatric ratings were performed prior to medication, midway in the study, and at the end of the study. Both the psychologic test battery and the global rating of improvement indicated a higher degree of improvement for

trifluperidol patients. Side effects of weight gain, sedation, and orthostatic hypotension were minimal for trifluperidol patients, but the incidence of extrapyramidal phenomena was higher for trifluperidol than for chlorpromazine (14 of 18 patients as opposed to 9 of 18 patients). Trifluperidol is the drug of choice for chronic schizophrenics. Suggested initial dosage is 0.5 mg daily, with dosage increments of 0.5 mg daily at 3- to 4-day intervals until improvement occurs; dosage should not exceed 6 to 8 mg daily.

Tulane University School of Medicine
New Orleans, Louisiana

901 Barsa, Joseph A. & Saunders, John C. **Tybamate, a new tranquilizer.** American Journal of Psychiatry, 120:492-493, 1963.

Tybamate, an analog of meprobomate, was tested in 43 chronically disturbed female psychotic patients, aged 16 to 71 years, for sedative effect. The antipsychotic agents that the patients had been taking were continued, but all sedative drugs were withdrawn and replaced by tybamate at an initial dose of 250 mg q.i.d. Dosage was increased until improvement was achieved or side effects appeared; the highest dose was 1,500 mg q.i.d. Patients remained on tybamate for 3 to 7 months. After this study, the sedative effect of tybamate was compared with that of meprobamate (400 to 1,200 mg q.i.d.) in a crossover study. Tybamate, when combined with antipsychotic drugs, was effective in relieving tension and anxiety. Its sedative properties were greater than those of emylcamate, but were less than those of meprobamate. Tybamate is suggested for use with patients whose tension and anxiety are not severe, or in whom the preservation of mental alertness is very important.

Rockland State Hospital
Orangeburg, New York

902 Friedman, Alice R. **Rorschach responses and treatment results under drug and group psychotherapy.** Acta Psychotherapeutics, 11(1):28-32, 1963.

A group of patients were given a group Rorschach test when they were started on combined group psychotherapy and drug therapy, and were retested 18 months to 2 years later. The time lapse allowed the results of the therapy to take hold and be maintained. In the cases reviewed, the tests showed improvement of mental controls, better form of perception, and elimination of the most bizzarre forms of thinking as expressed in the pretreatment tests. Increases also were noted in "popular" concepts of thinking and in more adequate form responses. Elimination of exaggerated repetitiveness of thinking resulted, enabling discharge of the patients. (The drugs used are not identified.)

752 West End Avenue
New York, New York

903 Johnson, Merlin H. & Davis, John R. **Electroshock and thioridazine therapy in the presence of glaucoma.** American Journal of Psychiatry, 120:397-398, 1963.

This report concerns the treatment of a severe depression in a 52-year-old man who had a complicating illness of narrow-angle glaucoma, which precludes the use of antidepressants because of their atropine-like side effects. With some anxiety, treatment with EST was decided upon. Before treatment, the subject's mean intraocular pressure was 36 mm Hg (normal pressure is 15 to 25 mm). Pilocarpine eye drops were given for the glaucoma. Then, one-half hour before EST, 500 mg acetozolamide in sodium bicarbonate solution was given p.o.; 14 mg succinylcholine chloride was given also i.v. at the time of EST. Pilocarpine eye drops were continued throughout the 10 EST treatments. The treatments were without incident, and the response was excellent except for rather severe confusion. Ten days after the last treatment, thioridazine was given in dosages up to 800 mg/day; dosage was reduced 25 days after its institution, and was eliminated after 43 days, with all symptoms cleared. During EST, normal intraocular pressures developed that rose when the symptoms reappeared and dropped again after treatment with thioridazine. The therapy outlined in this report is concluded to be safe as far as the ocular disease is concerned.

University of Washington School of Medicine
Seattle, Washington

904 Heyder, Dietrich W. **LSD-25 in conversion reaction.** American Journal of Psychiatry, 120:396-397, 1963.

In a welding accident, a 32-year-old man suffered burns on his right hand. He later complained of immobility of the right arm and

hand. A physical examination proved that there were no muscular or neurological abnormalities, and he was referred to a psychiatrist. Efforts to explore the problem were resisted by the patient, who denied any emotional conflicts and lacked insight as to possible psychological conflicts. The diagnosis of conversion reaction was made. After 1 year, the patient finally submitted to treatment---sodium amytal was given i.v. and the patient revealed three unfortunate incidents relating to his right arm. These incidents had occurred when he was a combat soldier in Korea and when he was a Chinese prisoner of war. The abreaction of self-accusatory feelings under sodium amytal improved the mobility of his arm, but shifted the symptoms to severe muscular pains in the neck. When the subject returned to work and the accident was discussed, the arm became stiff and hard again. Psychotherapeutic efforts were of no avail, and as a last resort, 300 g of LSD-25 were given three times in 8 days. There was little communication during the first two sessions, but on the third, motor hyperactivity, verbilization, and hallucinations occurred. The patient regained complete freedom of movement in the right arm. Administration of LSD-25 in a chronic conversion reaction points to another area of investigation---chronic traumatic neuroses---where the value of the drug is in its power to bring about an abreaction that could not be achieved by traditional methods.

Norfolk Mental Health Center
Norfolk, Virginia

905 Rose, J. T., Leahy, M. R., & Plowman, R. **A comparison of phenoxypropazine and amytryptiline in depression.** American Journal of Psychiatry, 120:393-395, 1963.

Phenoxypropazine was compared with amitryptiline in the treatment of 78 female patients who were hospitalized with primary depressive disorders. Phenoxypropazine was given 5 mg t.i.d. for 1 week, then 10 mg b.i.d. for 3 weeks; amytryptiline was given 25 mg t.i.d., then 50 mg t.i.d. for 3 weeks. To relieve anxiety produced by the antidepressant drugs, all patients received thioridazine 50 mg t.i.d. and a nightly dose of barbiturate. Forty patients, aged 20 to 72 years, received phenoxypropazine; 38 patients, aged 19 to 74 years, received amitryptiline. Phenoxypropazine was found to be as effective as amitryptiline in both reactive and endogenous depressions. The following side effects were seen: ankle edema (3 patients on phenoxypropazine), an erythematous rash (2 patients on amitryptiline), and mild transient hypotension (2 on phenoxypropazine and 4 on amitryptiline).

Walton Hospital
Liverpool, England

906 Danik, J. J. & Goverdham, M. **Haloperidol in the treatment of 120 psychotic patients.** American Journal of Psychiatry, 120:389-391, 1963.

Haloperidol was tested in 120 patients, 60 male and 60 female, 18 to 72 years of age, for the treatment of early and chronic schizophrenia. Dosage of the drug was started at 1.5 mg p.o. and was increased by 1.5 mg every 4 days until improvement or side effects were observed. Dosage was then reduced by 1.5 mg at weekly intervals until the optimum maintenance dose (usually between 0.75 and 3.0 mg daily) was reached. In some cases, initial treatment was with i.m. or i.v. injection of 10 mg haloperidol on alternate days. Dosage was again reduced to an effective maintenance dose. Sixteen early and 34 chronic schizophrenics showed good response. All but two of the good-response group were paranoid schizophrenic; the two exceptions were a catatonic schizophrenic and a schizo-affective psychotic. All other types of schizophrenics failed to respond to haloperidol treatment. Six patients with acute mania made an excellent response to haloperidol. Side effects were primarily extrapyramidal and took the form of motor restlessness (50% of the patients), dystonic reactions (40 patients), and pseudoparkinsonism (7 patients). Response to haloperidol usually occurs within 24 hours.

The Towers Hospital
Leicester, England

907 Nutys, A. **The treatment of chronic psychoses with dipiperon-R 3345.** Acta Neurologica et psychiatrica Belgica, 63:326-332, 1963.

Dipiperon, a member of the butyrophenone series, was tested in 47 female patients, aged 24 to 72 years, with severe psychotic symptoms of long duration. Forty-three of the patients had various types of schizophrenia, two had schizoid personalities, one was agitated and retarded, and one was a senile paranoid. The trial was carried out in two phases. In the first phase, all the patients received 40 to 400 mg dipiperon p.o. daily for 2 weeks to 5 months. Ten patients

showed significant improvement. In the second phase, these 10 patients were switched back to their former medication. Six regressed, and were again given dipiperon in maintenance doses of from 80 to 240 mg daily. Major improvements were in autism, activity, sleep, reactions to hallucinations and delusions, and the hallucinations and delusions themselves, which disappeared in a few patients. Paraphrenics showed the best response. Hypotension was the most important side effect; it appeared in all but 17 patients. Ten patients showed varying degrees of drowsiness and fatigue; a Parkinson-like syndrome was seen in nine patients.

Bethaniënhuis
St. Antonius-Brecht, Belgium

908 Lear, Erwin, Chiron, Albert E., & Pallin, Irving M. **Propiomazine hydrochloride in preanesthetic medication.** New York State Journal of Medicine, 63:409-414, 1963.

A blind study was made of propiomazine hydrochloride as preanesthetic medication in 466 surgical patients. Two-hundred patients (Group I) received 10 to 40 mg propiomazine HCl 2 hours preoperatively, as well as 12.5 to 50 mg meperidine HCl and 0.2 to 0.4 mg atropine 1 hour preoperatively. One-hundred sixty-five patients (Group II) received propiomazine HCl, meperidine HCl, and atropine, in the same dosages received by Group I, 1 hour preoperatively. The rest of the patients (Group III) served as controls and received graded doses of meperidine HCl 1 hour preoperatively. All medication was given i.m. Propiomazine HCl administered 2 hours before operation provided preanesthetic sedation comparable to that from the conventional regimen, which contained twice the amount of narcotic. The administration of propiomazine HCl, with narcotic and atropine, 1 hour before induction was less satisfactory. Nausea and vomiting were no more frequent, and the incidence and duration of postoperative hypotension were no greater when propiomazine HCl was administered 2 hours before operation than after the standard medication. Sixty-eight additional patients undergoing spinal anesthesia received propiomazine HCl i.v. A light sleep ensued, comparable to that resulting when pentobarbital is administered. Restlessness occurred in a few patients. Severe and prolonged hypotension was noted in two patients.

Jewish Hospital of Brooklyn
Brooklyn, New York

909 McCray, W. E., Hawkins, W. A., Kirkpatrick, W. L., & McGovern, W. J. **Long-term drug treatment of psychiatric outpatients.** Diseases of the Nervous System, 24:167-172, 1963.

A series of 114 female and 56 male outpatients whose ages ranged from 12 to 78 years were treated over a 52-week period with chlorprothixene. Most of the population were psychotic, with a predominant symptom of depression, which in several instances was suicidal. About 140 patients had previously been treated with ECT and/or drugs; all but 80 of the patients received other drugs or ECT or both during the study. Dosage was in a range of 30 to 400 mg daily, undivided doses for 162 patients; the remaining 8 patients received doses of up to 800 mg. Most patients (107) remained on the drug for 2 months or more. The results of chlorprothixene therapy showed patient response as follows: 27 excellent, 59 good, 37 fair, and 42 poor. There were five dropouts. Fifteen excellent and 22 good responses were obtained with chlorprothixene as the sole therapy. The drug was better in acute and paranoid schizophrenias than in the chronic type. Good response was also found in the schizoaffective patients and in the depressed manic-depressives. There were 25 side effects, including drowsiness, dizziness, nausea, and skin rash, reported by 36 patients, and the drug was discontinued in 16 of these cases. In the other 20 patients, the side reactions subsided, usually without reduction of dosage.

Lafayette Mental Health Treatment Center
Lafayette, Louisiana

910 Azima, H., Arthurs, Dorothy, Silver, A., & Azima, Fern J. **The effect of MP-809 in depressive states: A multi-blind study.** American Journal of Psychiatry, 119: 573-574, 1962.

The effectiveness of a tryptamine derivative, MP-809, was investigated in 50 depressed patients who were compared with two other similar groups receiving inert placebo and potent (phenobarbital) placebo. Each group consisted of 31 neurotic and 19 psychotic depressions. The MP-809 was administered with dosage regime of "gradual increase," with an average daily dose of 60 mg (dosage range from 20 to 100 mg) for an average period of 21 days. Potent placebo was given with an average daily dose of 30 mg. Treatment duration with both placebos averaged 21 days. In the MP-809 group, 26 patients showed moderate

to marked improvement, and 23 of 31 neurotic depressions improved. The drug seemed to have little effect in schizophrenic apathy and retardation. Chi-square analysis showed that comparison of drug with the two placebos was significant, particularly in neurotic depressions. Side effects were mild, consisting of fine hand tremors (10), drowsiness (8), weakness (6), dizziness (5), fatigue (4), nausea and vomiting (5), generalized pruritis (2), diarrhea (2), and ankle edema (1).

McGill University
Montreal, Canada

911 Gould, Arnold H. **Combined dexbrompheniramine-fluphenazine (Diperm Chronotab) in the oral treatment of pruritus.** Journal of New Drugs, 2:179-182, 1962.

Oral antipruritic therapy with a repeat-action tablet of dexbrompheniramine (6 mg)--fluphenazine (0.5 mg) was evaluated. Neither clinical nor laboratory evidence of intolerance was observed in preliminary short-term trials of the preparation in 34 patients with various pruritic conditions, or throughout longer trials (3 tablets daily for 30 days) in 10 healthy adult volunteers. A double-blind comparison of dexbrompheniramine--fluphenazine and sustained-release trimeprazine (as reference drug) was undertaken in 97 adults and older children with diverse itching dermatoses. Double-blind crossover trials of both drugs were carried out in 47 patients and double-blind trials of either drug in 50 patients. Complete or marked relief of itching was noted in 85 percent of the dexbrompheniramine--fluphenazine trials, and in 59 percent of the trimeprazine trials. Itching was unrelieved in only six percent of the trials with the test drugs, whereas trimeprazine was without benefit in 30 percent of its trials. Only minor side effects, mainly mild drowsiness, were observed in about 10 percent of the trials with either drug.

1635 Massachusetts Avenue, NW.
Washington, D.C.

912 Hollister, Leo E., Overall, John E., Caffey, Eugene, Bennett, J. L., Meyer, Fred, Kimbell, Isham, & Honigfeld, Gilbert. **Controlled comparison of haloperidol with thiorpropazate in newly admitted schizophrenics.** Journal of Nervous and Mental Disease, 135(6):544-549, 1962.

Haloperidol was compared with thiopropazate in a controlled clinical study of 112 newly admitted, schizophrenic men in five Veterans Administration hospitals. A fixed dose of drug was used during the first 2 weeks of treatment, and flexible doses were used thereafter; mean daily doses of drug used during the latter period were 8 mg of haloperidol and 80 mg of thiopropazate. Ratings were accomplished before treatment and at 6 and 12 weeks on the Brief Psychiatric Rating Scale (BPRS) based on psychiatric interviews, by Nurse's Evaluation Forms completed weekly, and by global estimates of clinical change. Data were complete on 96 patients treated for 6 weeks and for 56 patients treated for 12 weeks. After 6 and 12 weeks of treatment, both drug groups had improved significantly from pretreatment levels, with no significant differences being found between the two drugs. Major improvement indicated by the BPRS was in symptoms of emotional withdrawal, conceptual disorganization, mannerisms and posturing, hostility, suspiciousness, hallucinatory behavior, and uncooperativeness. Trends shown by the weekly ratings by nurses indicated that most improvement occurred early, with a leveling of change after 4 weeks. Global ratings showed clinically significant improvement in 53 percent of patients treated with thiopropazate and in 57 percent of those treated with haloperidol. In treating schizophrenics, haloperidol appeared to be somewhat more effective in the nonparanoid and thiopropazate was more effective in the paranoid. Only four patients left the study for medical reasons; side-effects and abnormal laboratory findings were not troublesome. (Author abstract, edited)

Veterans Administration Hospital
Palo Alto, California

913 Fishback, David B. & Castor, Louis H. **Effective hypertension therapy with least side effects: Observations on mebutamate and hydrochlorothiazide.** Journal of the American Geriatrics Society, 11(5):432-438, 1963.

A study was made in 50 patients, 33 female and 17 male, with established essential benign hypertension in mild to severe degree to determine the antihypertensive effectiveness of mebutamate, either alone or in combination with hydrochlorothiazide. Twelve patients received mebutamate for 2 to 5 months in doses of 300 mg/tablet q.i.d. Dosage was reduced to 300 mg b.i.d. if side effects warranted it. Blood pressure was reduced from an average of 196/100 to 170/93 mm Hg during treatment. Best results were achieved in

cases of early hypertension, without substantial renal or vascular changes. Thirty-eight patients were treated for 2 to 11 months with tablets containing 300 mg mebutamate and 25 mg hydrochlorothiazide; dosage was two tablets daily, one before breakfast and one before lunch. Blood pressure was reduced from 200/109 to 165/91 mm Hg. Results were fair to good in 75% of the mebutamate patients and in 90% of the patients taking the combination. Of 12 patients on mebutamate, 4 experienced mild drowsiness, 1 complained of nausea, and 1 complained of anorexia. Of 38 patients on the combination, 18 experienced mild drowsiness and weakness and 4 complained of dizziness. In elderly patients, half-strength tablets containing 150 mg mebutamate and 12.5 mg hydrochlorothiazide b.i.d. or t.i.d. had sufficient antihypertensive effect and produced almost no side effects.

Kensington Hospital
Philadelphia, Pennsylvania

See also: 925, 969

SIDE EFFECTS

914 Berthune, H. C., Burrell, R. H., & Culpan, R. H. **Headache associated with monoamine oxidase inhibitors.** (Letter) Lancet, 2(7319):1233, 1963.

A 5 to 10 percent incidence of severe headache is reported among patients receiving tranylcypromine. Phenelzine also produces headache in some patients. Intravenous phentolamine (5 mg) appears to be helpful in treating headache associated with MAO inhibitors; intravenous amylobarbitone sodium (0.5 g) is also helpful in some cases.

Auckland, New Zealand

915 Greene, Doreen. **Tranylcypromine.** (Letter) Lancet, 2(7307):586, 1963.

A case of intracranial bleeding, probably associated with tranylcypromine administration, is described. A 67-year-old man, who had been treated for depression with various drugs, was started on tranylcypromine and trifluoperazine by his physician. Two weeks later, he was stricken with a severe headache that continued and was associated with severe neck stiffness. When a clinical diagnosis of subarachnoid hemorrhage was made, the patient was admitted to a hospital. When admitted, he had a blood-pressure reading of 140/80 mm Hg, severe neck stiffness, and a positive Kernig's sign. A lumbar puncture showed the cerebrospinal fluid to be xanthochromic, with total protein 90 mg/100 ml, moderate excess of gloublin, 50 red cells/cmm, and less than three lymphocytes per cmm. The EEG and skull X-ray were normal. The headache persisted for 14 days, and back pain continued for 2 more weeks. Eventual recovery was complete.

National Temperance Hospital
London, England

916 Arenillas, L. **Tranylcypromine.** (Letter) Lancet, 2(7307):586, 1963.

The possible association between eating cheese and development of severe headache in patients taking monoamine oxidase inhibitors is questioned. Discussed briefly are five cases of patients who had attacks of severe headache while taking tranylcypromine or phenelzine. In no case could the onset of headache be connected with the ingestion of cheese. Nine other patients on tranylcypromine did not develop the severe-headache side effect. Of these, four ate cheese 1 to 4 times a day, and two ate cheese almost every day. From this series of patients, there is no clear relation between eating cheese and the typical side effects of tranylcypromine.

Hill End Hospital
St. Albans, England

917 Anglade, Fraillon, Darchary, & Richou. **Intoxication suraiguë par ingestion massive d'imipramine. (Extremely acute intoxication due to massive ingestion of imipramine.)** Annales Médico-Psychologiques, 121:262-265, 1963.

A fatal case of massive ingestion of imipramine by a 24-year-old female depressive is described, and 10 cases in the literature of massive ingestion of imipramine are reviewed. The patient ingested 100 tablets of imipramine at approximately 7:30 A.M. and came to the clinic at 10:40 A.M. She showed tituba-tion, but had good spatio-temporal orientation; she grew progressively worse and died at 5:00 P.M. in a state of profound collapse. In the 10 cases reviewed, 1,000 to 3,750 mg imipramine had been ingested in suicidal attempts. Most authors reported rapid appearance of coma, tendency toward cardiovascular collapse, frequent convulsive crises, hypothermy, mydriasis, and hyperreflectivity of the tendons. They also pointed out the absence of a specific antidote and the necessity of purely symptomatic treatment. It appears that prognosis is favorable up to approximately 1,500 mg, but deteriorates thereafter. Complete recovery without sequela in favorable cases indicates lack of specific toxicity of imipramine. The present authors made the following original observations concerning the course of imipramine poisoning: a latent period between ingestion of the drug and appearance of symptoms; hyperthermy, which may be an indication of the gravity of prognosis; and, the primitive oneiric-confu-

sion phase. It is recommended that no more than 50 tablets be prescribed at one time to limit the possibility of acute intoxication.

(No address)

918 Häfner, H. & Brehm, I. **Thrombosen und embolien als Komplikationen der Behandlung mit Psychopharmaka. (Thromboses and embolies as complications of psychopharmacological treatment.)** Fortschritte Der Medizin, 81(12):491-496, 1963.

A retrospective study was done of 1,590 patients (969 females and 621 males) who received neuroleptic and antidepressive therapy between 1958 and 1961. Patients taking at least 75 mg chlorpromazine, 3 mg reserpine, or an equivalent effective dose of another neuroleptic for at least 10 days were selected. The average dose was relatively high. Patients on tranquilizers and MAO inhibitors were not included. Thromboses and emboli were studied for side effects. Of the 1,590 patients, 49 (3.1%) had thromboses, thrombophlebites, and thromboemboli. Of these, nine (18%) were fatal. Of the 40 nonfatal cases, 3 patients had acute lung emboli with infarct pneumonia. Thromboses were localized mainly in the leg veins, but seven patients showed atypical localization. Of the 49 patients, 24 had previous illnesses that may be considered as predisposing factors (heart trouble in 7, hypertonia and arteriosclerosis in 8, varicosis and secondary anemia in 3, puerperal complications in 1, and myocardial infarct in 1). Thromboses and emboli were found in a high proportion (8.6%) of patients in the 61- to 70-year age group. There was no significant difference between the sexes in fatal cases, although females predominated in nonfatal cases. No clear relationship to psychiatric diagnosis or condition was found. Of the 49 cases, 35 had undergone sleep therapy with large doses of neuroplegics. Ten others had been confined to bed during the week preceding appearance of the complications. The etiological factor is undoubtedly massive neuroplegia, most often accompanied by bed rest or sleep therapy.

University of Heidelberg
Heidelberg, Germany

919 Roberts, Eugene, Simonsen, Daisy G., & Roberts, Ethel. **Arginine protection against hydrazine toxicity.** Biochemical Pharmacology, 12:1445-1447, 1963.

The protective action of arginine against hydrazine toxicity was tested in male mice (25 to 35 g). A dose of 6 mmoles of l-arginine/kg was given i.p. 30 minutes prior to injection of 3 mmoles/kg of hydrazine; control mice received saline prior to hydrazine. Mortality was greatly reduced in the l-arginine mice, and there was a reduction in total seizure incidence, usually less than 40% of the test animals showing any seizure activity during the observation period. Doses of 1.28, 2.56, 3.84, and 5.12 mmoles/kg l-arginine were also tested. There was a marked protective effect in all groups. The effect of l-arginine appeared to be stereospecific, since d-arginine showed no protection. Arginine solutions given i.v. after normally fatal doses of hydrazine prevented seizures and allowed the animal to survive. Arginine is effective as both a therapeutic and prophylactic agent against hydrazine.

City of Hope Medical Center
Duarte, California

920 Ayd, Frank J. **Prolonged perphenazine therapy and thyroid function.** American Journal of Psychiatry, 120:592-594, 1963.

From among 100 chronically ill, ambulatory psychiatric patients who had been taking perphenazine for a miminum of 3 years, 25 were randomly selected for protein bound iodine (PBI) studies. Each patient was physically healthy and showed no signs of thyrotoxicosis. The group consisted of 10 men and 15 women (mean age, 40 years). The minimum dosage of perphenazine taken was 3,878 mg and the maximum was 48,944 mg (mean dosage, 15,609 mg). Twenty-two patients had normal PBI values (4.0 to 8.0 mcg/100 cc); 2 patients had a value of 8.3 mcg/100 cc; and 1 patient had a value of 3.9 mcg/100 cc. Phenothiazine has no direct or indirect pathological influence on the thyroid gland.

Baltimore 12, Maryland

921 Wilson, Ian C. **Status epilepticus associated with withdrawal from Deprol (meprobamate and benactyzine).** American Journal of Psychiatry, 120:600-601, 1963.

A case of status epilepticus that occurred on withdrawal from excessive doses of meprobamate--benactyzine is described. A female patient, aged 44 years, with no history of epilepsy, but with two previous hospital admissions for manic-depressive reaction (depressed type), entered the hospital again in

a state of retarded depression. Shortly before admission, she was taking 18 to 20 meprobamate--benactyzine tablets daily. On admission, she became agitated and tremulous and had episodes of vomiting. After receiving phenobarbital (120 mg i.m.), her tremors became more severe, and she appeared to be in an acute delirious state She was placed on a regime of diphenylhydantoin sodium (100 mg), phenobarbital (30 mg), and thioridazine (100 mg), each t.i.d. Another injection of phenobarbital (120 mg) caused little modification in tremulousness, and a few hours later, she began to have grand mal convulsive seizures, which became more frequent, and she went into a status epilepticus. She was immediately given paraldehyde (5 cc i.m.) and an enema, followed by 5 cc paraldehyde in 30 minutes, and then 5 cc at hourly intervals. This regime barely modified the incidence and severity of convulsions. About 5 hours after the initial convulsion, during a period of consciousness, 2 meprobamate--benactyzine tablets were given orally. Within 1 hour, convulsions ceased, tremors disappeared, and the patient began to reorient to her environment. A total of 10 meprobamate--benactyzine tablets daily were required to maintain the patient in a state of stability. This dosage was gradually reduced by 2 tablets/day every week. Too rapid reduction in dosage resulted in a return of tremors and agitation. A period of 3 months was required for complete withdrawal. The patients' EEG's following withdrawal and 6 months later were normal.

Broughton Hospital
Morganton, North Carolina

922 Dietze, H. J. **Dyskinetic syndrome associated with chlorprothixene.** American Journal of Psychiatry, 120:503-504, 1963.

A case is described in which a dyskinetic syndrome developed within an hour after a dose of chlorprothixene. A 13-year-old Negro boy (I.Q., 72) was admitted to the hospital showing signs of anxiety and motor restlessness. He was started on chlorprothixene, 25 mg t.i.d., which was later increased to 50 mg t.i.d. After 2 weeks, he suddenly developed a painful contraction of his neck muscles. He was unable to bend his head forward, was drooling, could not close his mouth, and his tongue was protruding. Romberg, Kernig, and Brudzinski were negative; blood pressure was 120/82, pulse was 80, and temperature was 96.8° F. Cranial nerves were intact with the exception of VII. Facial muscles, the trapezoid muscle, and the long muscles of the back were contracted. The sensory system was unimpaired. No pathological reflexes were found with the exception of a positive Myerson's sign. When chlorprothixene medication was discontinued and the patient was given sodium caffein--benzoate (2 cc i.m. in 2 doses), there was overnight improvement. Symptoms disappeared gradually during the day. The patient was then placed on chlordiazepoxide, and no further side effects were observed.

Governor Bacon Health Center
Delaware City, Delaware

923 McCurdy, R. Layton & Kane, Francis J., Jr. **Orthostatic hypotension associated with high dosage of librium.** American Journal of Psychiatry, 120:601-602, 1963.

An acutely intoxicated white male (37 years of age), with a previous history of alcoholism, was admitted to a hospital with a blood pressure of 134/80 and a pulse of 120 recumbent. Reflexes were mildly hyperactive, but other physical findings were within normal limits. The patient was started on chlordiazepoxide, 50 mg q.i.d., diphenylhydantoin 100 mg q.i.d., and a gastritis regimen. After accidental ingestion of solid food and the subsequent vomiting of blood, recumbent blood pressure was 155/95 and pulse was 96. The tremulousness increased, and the chlordiazepoxide dosage was changed to 125 mg six times daily. Marked standing hypotension and tachycardia continued, and complete bed rest was ordered. As tremulousness decreased, chlordiazepoxide was gradually reduced to 50 mg q.i.d. Orthostatic hypotension decreased over a 4-day period, the general condition improved, and the patient was discharged on the 14th hospital day.

University of North Carolina
Chapel Hill, North Carolina

924 Kramer, Milton. **Delirium as a complication of imipramine therapy in the aged.** American Journal of Psychiatry, 120: 502-503, 1963.

A 71-year-old white male with an intracranial tumor and a mild chronic brain syndrome was treated postoperatively with imipramine, 10 mg q.i.d. When the patient became weaker and more discouraged, the dosage was increased to 20 mg q.i.d. Four days later, the dosage was again increased to 50 mg t.i.d. The patient's condition deteriorated, and he became confused, irritable, agitated, and, at night, sleepless and incoherent. Imipramine was decreased to 20 mg q.i.d. and

stopped 2 days later. Symptoms gradually receded over a 6-day period, and the patient was discharged.

University of Cincinnati
Cincinnati, Ohio

925 Jotkowitz, Max W. & Gershon, Samuel. **Manic reactions following combined "Tofranil" (Imipramine) and electro-convulsive therapy.** Medical Journal of Australia, 6:87-90, 1963.

Three cases of mania induced by combined imipramine and ECT are presented. These patients were among 13 admitted to the psychiatric ward of a general hospital during a 17-week period. None of the patients was considered to be of cyclothymic temperament, and none was known to have exhibited any previous manic swings. A fourth case, in which imipramine--ECT produced activation of psychosis is also presented. The high incidence of mania (4 of 13 cases) suggests that imipramine and ECT may potentiate each other's action.

Prince Henry's Hospital
Melbourne, Australia

926 Gruber, Louis N., Chapman, W. Waddy, & Pratt-Thomas, H. Rawling. **Fatal toxic reaction to chlorpromazine (Thorazine).** Journal of the South Carolina Medical Association, 59:203-204, 1963.

A 77-year-old white woman, with a history of severe hypertension, old myocardial infarct, dizzy spells, and episodes of disorientation, was treated with chlorpromazine, from which there was a fatal toxic reaction. At the beginning of hospital treatment, the patient received 200 mg of chlorpromazine daily. On admission to a convalescent home, dosage was increased to 300 mg daily. Shortly after admission, she began to have intermittent fever, and mild jaundice appeared, which progressed steadily. Chlorpromazine was discontinued. She was transferred to the hospital in a semicomatose condition. Although the terminal event was a pulmonary embolus, it appears from the clinical course and pathologic findings that the patient would have died from hepatic injury alone. Hepatic sensitization is common during chlorpromazine treatment, but only a small number of patients become frankly jaundiced. There are only scattered reports of fatalities. The pathologic picture is dominated by intrahepatic biliary obstruction, particularly in the smaller centrilobular canaliculi, and is thought to be of allergic etiology. The toxic reaction described has been reported to occur after only a single dose of chlorpromazine, and, as in the present case, may progress after the drug is discontinued.

Medical College of South Carolina
Charleston, South Carolina

927 Clink, H. M. **Foetal death after promazine and pethidine.** (Letter) British Medical Journal, 2(5358):684, 1963.

Fetal death occurred after promazine and pethidine were given as sedation before surgical induction of labor. Although the drugs had previously been used successfully in such cases, in the case discussed, profound fetal distress appeared immediately following intravenous injection of drugs. The placenta weighed 1 pound 9 ounces, its gross appearance was healthy, and the histology was normal.

Royal Free Hospital
London, N.W.3., England

928 Paterson, M. C. **Addiction to "drinamyl".** (Letter) British Medical Journal, 2(5358):684, 1963.

People with disturbed personalities, who have become dependent upon dexamphetamine and amylobarbitone, will go to any lengths to obtain the drug. Particular care should be taken when a doctor is asked to accept a new patient, and, at the same time, a request is made for a prescription of dexamphetamine or amylobarbitone.

North London Magistrates Court
London N.16, England

929 Gates, J. C. **Reactions to tranylcypromine.** (Letter) British Medical Journal, 2(5358):683, 1963.

An oral diuretic given as part of tranylcypromine treatment is apparently successful in avoiding acute hypertensive reactions (violent occipital headache, projectile vomiting, and stiffness and acute tactile sensitivity of neck muscles). Recovery appears to be followed by a spontaneous diuresis. One case admitted to hospital as a suspected

subarachnoid hemorrhage showed normal serum electrolytes and cerebrospinal fluid biochemistry. The hypertensive reactions were also observed in three patients taking phenelzine. Clinical observations indicate that the lifelong endogenous depressive is much less likely to get a reaction to the drug than the neurotic depressive, possibly because of a permanent need of monoamine oxidase inhibitor to correct some abnormality, whereas with neurotic depression, a possibly toxic excess of the drug develops.

East Looe
Cornwall, England

930 Dorrell, W. **Tranylcypromine and intracranial bleeding.** (Letter) Lancet, 2(7302):300, 1963.

In the third case of intracranial bleeding in patients treated with tranylcypromine (in whom neurosurgical investigations showed no evidence of aneurism) a 38-year-old male patient, complaining of feelings of unreality, was given tranylcypromine 10 mg and trifluoperazine 1 mg t.i.d., and the prescription was repeated 1 month later. Two days later, severe bitemporal headache developed due to a left hemiplegia. On lumbar puncture, blood clotted in the manometer. No carotid abnormality was found, but lumbar air encephalography showed displacement of the septum pellucidum to the left and asymmetry of the anterior part of the lateral ventricles, which was diagnosed as intracerebral hematoma. An air encephalogram performed 4 months later was normal.

The Middlesex Hospital
London, W. 1., England

931 Milligan, W. Liddell. **Tranylcypromine.** (Letter) Lancet, 1(7278):442, 1963.

Nonsevere headache occurred in 3 percent of more than 1,000 patients who were treated with the combination of tranylcypromine sulfate (10 mg) and trifluoperazine (1 mg). Fifty general practitioners, who had used the drug in over 1,000 cases, reported only a few instances of side effects and no case of severe occipital headache.

St. James's Hospital
Portsmouth, England

932 McQuaker, William. **Tranylcypromine.** (Letter) Lancet, 1(7278):442, 1963.

A case is described in which the administration of tranylcypromine was accompanied by neurological disturbances. Tranylcypromine was prescribed for a woman, age 60 years, who was admitted to hospital in a state of depression accompanied by retardation. Three hours after receiving her second dose (i.e., after a total of 20 mg), violent twitching of the left foot and left arm occurred. Some 10 minutes from the onset, the left leg and left arm were jerking violently; the head and eyes were turned to the left, and the blood pressure was 180/120 mm Hg. Breathing became stertorous. Paraldehyde was given intramuscularly, and gradually the jerking ceased and her breathing became normal. After 48 hours, the patient seemed completely normal. She had taken no drugs of any sort for at least 4 weeks before admission, and tranylcypromine only was given before the neurological disturbances occurred.

Warlingham Park Hospital
Warlingham, Surrey, England

933 Weber, J. C. P. **Tranylcypromine and cheese.** (Letter) Lancet, 2(7307):587, 1963.

The possible relationship between cheese and tranylcypromine in provoking hypertensive attacks is being investigated, but there is presently no conclusive proof of cause and effect. Physicians are urged to report any evidence or information which might assist in the investigation.

Smith Kline and French Laboratories, Ltd.
Welwyn Garden City, England

934 Read, A. E. A. & Arora, B. **Tranylcypromine and cheese.** (Letter) Lancet, 2(7307):587, 1963.

An early report of headache induced by a tranylcypromine--cheese combination was made by a patient who did not succeed in convincing her doctor of the relationship.

University Department of Medicine
Bristol, England

935 Foster, A. R. **Tranylcypromine and cheese.** (Letter) Lancet, 2(7307):587, 1963.

The question of a connection between the taking of tranylcypromine together with the eating of cheese and the onset of severe headaches is explored. Twenty-five such observations were seen by the author, and he now has the impression that when cheese is avoided, fewer headaches occur. If the assumption of some form of trigger mechanism is correct, the incidence of this side effect should be greatly reduced. In addition tranylcypromine combined with trifluoperazine is valuable in treating depressive illness.

Exe Vale Hospital
Exminster, near Exeter, Devon

936 Enoch, M. David. **Tranylcypromine.** (Letter) Lancet, 2(7305):463-464, 1963.

A case history is reported of death from intracranial bleeding in a 38-year-old woman taking tranylcypromine. The patient was taking 1 tablet t.i.d. of a tranylcypromine preparation for treatment of reactive depression when her symptoms began. When admitted to the hospital, she was comatose and restless; neurological signs included bilateral dilated pupils, exaggerated reflexes, and extensor plantar response. The patient died 12 hours after symptoms began. In previous cases of intracranial bleeding in patients on tranylcypromine, bleeding was massive and associated with some lesion or abnormality, or with the giving of another amphetamine derivative. In the present case, bleeding was macroscopic, but not massive, was not associated with any lesion or abnormality, nor was any other amphetamine derivative being given simultaneously. Petechial hemorrhages in vital centers were regarded as the cause of death. The woman had complained of severe headaches, and her systolic blood pressure was 170 mm Hg.

Shelton Hospital
Shrewsbury, England

937 Tuller, Martin A. & Cohen, Irwin R. **Tranylcypromine.** (Letter) Lancet, 2(7305):464, 1963.

A case history is reported in which tranylcypromine caused remission of acute intermittent porphyria in a 36-year-old woman. Tranylcypromine, 10 mg b.i.d., was given to relieve depression; within 24 hours, the patient's nausea and depression disappeared. Dosage was reduced to 10 mg daily, then to 10 mg every third day, and then to 10 mg every fourth day. Eventually, the patient was able to discontinue the drug, and has continued to be well, although porphobilinogen is still present in the urine.

Jamaica, New York

938 Davies, E. Beresford. **Combining the antidepressant drugs.** (Letter) Lancet, 2(7311):781-782, 1963.

Various combinations of almost all of the psychotropic drugs were used to treat many hundreds of patients with serious or prolonged depressions in the past 5 years without fatality. Dexamphetamine may be given safely in conjunction with imipramine, amitriptyline, or a monoamine oxidase inhibitor to many patients for months, although the combination may be unsuitable in individual cases. Pheniprazine and etryptamine are no longer used, and the use of phenoxypropazine and iproniazid is in doubt, even though some patients have responded to one or other of these drugs only. It seems highly probable that tranylcypromine, in conjunction with exogenous factors, such as food, drink, or certain infections (e.g., influenza), is causally associated with subarachnoid hemorrhage.

Addenbrooke's Hospital
Cambridge, England

939 Boardman, R. H. **Combining the antidepressant drugs.** (Letter) Lancet, 2(7311):782, 1963.

An argument is put forth in favor of prescribing several antidepressant drugs in combination for treatment of mental illness. Additional drugs are given to inhibit or enhance particular effects of a certain drug. In an organ as complicated as the brain, a single drug possessing all the necessary attributes is not likely.

Parkside Hospital
Macclesfield, England

940 Schrire, I. **Collapse after "parstelin".** (Letter) British Medical Journal, 2(5359):748, 1963.

In answer to a letter describing a fatal reaction attributed to a tranylcypromine—trifluoperazine preparation, it is suggested that, from the circumstances described, death could more likely be attributed to the residual effect of the MAO inhibitor previously prescribed, enhancing the tranylcypromine effect. The patient had been receiving iproniazid and was then switched to the tranylcypromine preparation without any drug-free interval. Cumulative effects producing symptoms of overdosage are quite possible when tranylcypromine is given to a patient who has been taking another MAO inhibitor, unless a 1-week treatment-free interval is imposed. The conclusion that the patient's death was due to the tranylcypromine preparation is scientifically unsound.

Smith Kline and French Laboratories, Ltd.
Welwyn Garden City, England

941 Lantin, H. **Collapse after "parstelin".** (Letter: comment on letter by G. A. Low-Beer and D. Tidmarsh.) British Medical Journal, 2(5363):998, 1963.

A reply is given to a letter reporting a tranylcypromine preparation as the cause of death in a patient. The patient had been receiving iproniazid for 3 weeks prior to tranylcypromine administration. Excretion of MAO inhibitors is delayed; resulting in their presence in the body up to 7 days after cessation of treatment; the MAO inhibitors are known to potentiate the action of other MAO inhibitors and CNS depressants. It is suggested that iproniazid may have been responsible, in part, for the patient's death rather than the tranylcypromine preparation alone or in combination with ephedrine.

London, SW. 19, England

942 Cooper, A. J. & Rose, M. J. **Subarachnoid haemorrhage after tranylcypromine.** (Letter) British Medical Journal, 2(5359): 747-748, 1963.

A case of subarachnoid hemorrhage is reported in a male patient receiving 40 mg tranylcypromine daily. The patient developed symptoms on the 24th day of tranylcypromine therapy. Blood pressure was 180/110 mm Hg (normally 130/80); pupils were widely dilated, equal, and did not react to light; tendon jerks were exaggerated; abdominal reflexes were absent; and there were bilateral extensor plantar responses. After lumbar puncture, the patient improved. Two months after the subarachnoid hemorrhage, angiography showed a normal cerebrovascular tree.

Barrow Hospital
Barrow Gurney, England

943 Burke, C. W. **Collapse after "parstelin".** (Letter: comment on letters by J. C. Gates, G. A. Low-Beer, and D. Tidmarsh.) British Medical Journal, 2(5363): 998, 1963.

A reply is presented to two letters on the side effects of tranylcypromine. The first letter concerns fluid retention and diuresis during tranylcypromine therapy, and the second letter reports a death due to a tranylcypromine preparation. Fluid retention does occur, but it is rare and not associated with paroxysmal side effects. The diuresis reported was not seen in four other cases; the sudden voiding of large quantities of urine after an attack subsides is more likely to be due to extraneous factors, such as inhibition of the bladder due to fear during an attack. The reported death from the tranylcypromine preparation was more likely due to a synergistic effect between tranylcypromine and amphetamine or ephedrine. All three drugs are chemically and pharmacologically similar; all three inhibit monoamine oxidase, contain propylamine side chain, are CNS stimulants, and are sympathomimetic. Their side effects are identical, except that tranylcypromine causes those that are paroxysmal. Tranylcypromine should never be given within 1 to 2 weeks of giving ephedrine or amphetamine.

London, SW. 11, England

944 MacVicar, John. **Foetal death after pethidine and promazine.** (Letter) British Medical Journal, 2(5363):999, 1963.

The i.v. administration of pethidine and promazine (50 mg of each) to women in labor produced no serious effects in over 1,000 cases seen by the author. Higher dosage was not found to be necessary. When caesarean section is planned, it may be advisable to wait until drug effect subsides.

University of Glasgow
Glasgow, Scotland

945 Richmond, P. W. & Roberts, A. H. **Side-effects of tranylcypromine.** (Letter) British Medical Journal, 2(5363):999, 1963.

In 38 patient trials with tranylcypromine, in which dosage prescribed was 10 mg b.i.d. for 5 days and then 20 mg b.i.d., 15 patients experienced severe side effects and 9 experienced headache. Headache developed suddenly in some patients who had taken 40 mg daily for 3 to 12 weeks without trouble. In other patients, symptoms (including palpitations, visual disturbance, nausea, and drowsiness) occurred with doses of 20 to 30 mg daily within a week or two of starting medication. Tranylcypromine was an effective antidepressant, but not more so than isocarboxazid, which was relatively free from side effects.

Atkinson Morley's Hospital
London, England

946 Misiti, D., Rosnati, V., Bignami, G., Bovet-Nitti, F., & Bovet, D. **Effects of d,l-3-phthalimidoglutarimide and N-phthalyl-d,l-aspartimide on rat pregnancy.** (Letter) Journal of Medicinal Chemistry, 6(4):464-465, 1963.

The effects of two compounds, d,l-3-phthalimidoglutarimide (II) and N-phthalyl-d,l-aspartimide (III), that are closely related to thalidomide, were studied in pregnant rats. Reaction sequences for the synthesis of both compounds are given. Toxicity data for rats and mice are tabulated. The oral LD50's of thalidomide and compound II are > 10,000 mg/kg in both rats and mice; the oral LD50 for compound III is 3,500 mg/kg in mice and 5,000 mg/kg in rats. All three drugs were given to pregnant rats in daily doses of 500 mg/kg p.o. Administration of compound III and thalidomide during the first days of pregnancy resulted in failure of implantation in high proportion of treated animals. An increased incidence of resorption and a reduction of the mean fetal weight followed later administration of the three drugs. No malformations were noted with compounds II and III. All three drugs are teratogenic for chick embryo. It was conjectured that the adverse effects of thalidomide stemmed from faulty metabolism of a natural amino acid. Compound II, however, is an unnatural amino acid, yet it also produces adverse effects. From this, it seems doubtful that adverse effects on rat pregnancy are due solely to faulty metabolism of a natural amino acid.

Institute Superiore di Sanitá
Rome, Italy

947 Milligan, W. Liddell. **Collapse after "parstelin".** (Letter: comment on letter by G. A. Low-Beer and D. Tidmarsh.) British Medical Journal, 2(5360):807, 1963.

In a series of 1,200 patients treated with a tranylcypromine—trifluoperazine combination, about 3% complained of headache, and in only one case was this severe. Dosage prescribed for these patients generally did not exceed 2 tablets daily. For the 15 patients who required 3 tablets daily, treatment duration did not exceed 2 weeks.

St. James's Hospital
Portsmouth, England

948 Pilling, H. H. **Tranylcypromine and convulsions.** (Letter) British Medical Journal, 2(5365):1130, 1963.

In this correspondence, the author notes that although tranylcypromine seldom produces convulsions, in 2 years, 2 out of 20 patients developed temporary epilepsy with the drug. This phenomenon disappeared after treatment was withdrawn. To spare patients the inconveniences associated with this condition, this experience should be considered. In one of the two patients, after only one major convulsion, depression lifted and the patient felt better.

Sheffield 10, England

949 Bram, G. **Side-effects of tranylcypromine.** (Letter) British Medical Journal, 2(5369):1407, 1963.

The author states in this correspondence that the side effect of headache from the use of tranylcypromine had occurred in about 4% of his patients. These patients, on further investigation, have had a past history of suffering from various types of headaches. Upon withdrawal of the drug or a combination of the drug with trifluoperazine, the side effect stopped. Probably the level of circulating sympathomimetic amines, already disturbed by the drug, is raised by some exogenous or endogenous factor. Then a vascular storm is created in patients who are predisposed to cerebral vascular instability or in whom amine metabolism is constitutionally abnormal. To prevent the side effects, one should make sure that the patients have not been headache sufferers.

London, SE. 22, England

950 Pommé, B., Girard, J., & Gilbert, J. **Manifestations neurologiques au cours de l'intoxication chronique par les hydantoïdes.** (Neurological manifestations in chronic intoxication by hydantoides.) Annales Médico-Psychologiques, 2(5):707-710, 1962.

The diagnosis and handling of two cases of neurological attacks occurring among approximately 30 cases of epilepsy treated with hydantoin are described. The patients were a boy of 10 years old and a girl of 11 years old. Both had been on medication including 20 to 30 mg hydantoin per day (sedantoinal and di-hydan, respectively) for several months. Both children exhibited cerebellar ataxia. Absence of cerebellar tumor upon pneumoencephalography in the boy led to a diagnosis of hydantoin intoxication. Suppression of hydantoin medication produced rapid and complete regression of the cerebellar syndrome. Diagnosis is theoretically simple. Hydantoin intoxication is relatively rare and appears to be associated with prolonged therapy at high dosage. The first sign of intoxication is hypertrophic gingivitis. The neurological disturbance usually appears as cerebellar attack. Motor deficiency of the legs makes walking impossible, and muscular pains of the polyneuritic type sometimes are present. Tendinous reflexes are depressed to various degrees. Following suspension of treatment, the motor-sensory deficiency is the last sign to disappear.

(No address)

951 Davis, J. G. **Cheese and tranylcypromine.** (Letter) Lancet, 2(7318):1168, 1963.

In a further correspondence on cheese and tranylcypromine, the author notes that there might be a relationship between the severity of migraine and the type and age of cheese. Unripened cheese could give less reaction than the fully ripened, hard cheeses, the smear-ripened types, and the blue-veined cheeses. The four groups have an amine content that increases in the above-named order and, therefore, have much higher pH values. The amine content in milk and butter is normally negligible.

Gerrard Street
London, England

952 Howieson, W. E. **Cheese and migraine.** (Letter) Lancet, 2(7316):1063, 1963.

In one of the author's patients, frequent bouts of migraine in fluctuating severity occur within a few hours after the ingestion of cheese, and the "stronger" the cheese, the more severe the migraine. This side effect is more prominent in the menstrual period, when the patient takes prochlorperazine (5 mg t.i.d.). For several days after, the patient cannot tolerate milk or butter, although these do not precipitate or aggravate the migraine. This finding is compatible with other findings, suggesting that cheese contains sympatheticomimetic amines.

Fulbourn Hospital
Cambridge, England

953 Adams, P. H., Chalmers, T. M., & Davies, E. Beresford. **Tranylcypromine and acute intermittent porphyria.** (Letter) Lancet, 2(7309):692, 1963.

To supplement a previous report of an alarming reaction 36 hours after ingestion of tranylcypromine for the treatment of acute intermittent porphyria, the author discusses the case of a 54-year-old woman who was given tranylcypromine to relieve the persisting depression from the illness. Twenty-four hours after the first dosage, she felt unwell and detached; these symptoms increased until the patient was restless, flushed, sweating profusely, and talking incoherently. Upon admission to the hospital, after ingesting 70 mg of the drug in 36 hours, her temperature was 101° F, pulse was 130 bpm, and blood pressure was 190/120 mm Hg. Pupils were fixed and dilated, and coarse nystagmus, carpopedal spasm, clonus at the knees and ankles, and bilateral extensor responses were present. The drug was stopped, and the patient was given 100 mg chlorpromazine i.m. and 100 mg hydrocortisone i.v. The patient recovered 8 hours later. It is suggested that tranylcypromine was the responsible factor, either acting alone or indirectly by precipitating a porphyric crisis.

Addenbrooke's Hospital
Cambridge, England

954 **Tranylcypromine and cerebral haemorrhage.** Lancet, 2(7311):794, 1963.

In a letter sent to all doctors in this country, Smith, Kline & French, the manufacturers of Parnate (tranylcypromine) and Parstelin (tranylcypromine plus trifluoperazine), re-

port instances of cerebral hemorrhage in patients taking tranylcypromine. Doctors are advised to warn patients that symptoms such as persistent severe headache should be reported immediately. Severe reactions while taking the drug can be caused by cheese, as well as by alcohol. Therefore, patients should be told to avoid cheese and alcohol while they are taking tranylcypromine.

(No address)

955 Ehtishamuddin, M. **Tranylcypromine.** (Letter) Lancet, 2(7315):1015, 1963.

A case of a fatal reaction to tranylcypromine in a 39-year-old woman who was an amphetamine addict is reported. After being admitted to the hospital following an overdose of amphetamine, this drug was withdrawn, and she was given tranquilizers, which were followed later by a prescription of tranylcypromine (10 mg t.i.d.). On the latter drug, the patient developed rigors. On the eighth day of treatment, she was found unconscious after she had taken 16 tablets of tranylcypromine. She never regained consciousness and died 5 days later. Postmortem examination showed a hemorrhage 1-½ inches in diameter in the left frontal lobe and adjacent part of the parietal lobe. A little blood had entered the ventricles, and there was a small amount of blood staining of the subarachnoid space around the brain stem. There was no evidence of aneurysm or significant atheroma of the cerebral arteries.

Selly Oak Hospital
Birmingham, England

956 Barker, J. C. & Enoch, M. David. **Combining the antidepressant drugs.** (Letter) Lancet, 2(7309):691, 1963.

In this letter, the authors contest the claims made in a previous article by a Dr. Sargant, who advocates combining antidepressant drugs. They also question his statement that: (1) A patient should not suddenly die as a result of drugs that have been administered for a long period; and (2) It is safe to use different antidepressants consecutively with no long interval between. Generalized instances of fatalities and disastrous side effects from combinations, prolonged use, and immediate switching of various antidepressants are given. A more critical appraisal of drug action, through noting specifically which syndromes and symptoms respond to various drugs, is more valuable and less damaging than multiple prescribing.

Shelton Hospital
Shrewsbury, England

957 Davies, E. Beresford. **Tranylcypromine and cheese.** (Letter) Lancet, 2(7309): 691-692, 1963.

In connection with the symptoms produced from tranylcypromine and cheese, the author states that similar phenomena occurred in 1958 and in 1959 during a pilot trial with nialamide---out of 212 patients, 5 reported headache (4 were in association with intake of small quantities of alcohol, and 2 had evening meals of cheese). Since then, 14 additional cases of headache were found in patients on MAO inhibitors (nialamide, 4; phenelzine, 5; iproniazid, 3; and tranylcypromine, 2) after ingestion of cheese. The most common time of onset is after a meal, particularly the evening meal. Other symptoms have been transient malaise, mausea, and dizziness. These attacks have been prevented by withdrawal of alcohol and cheese from the diet, or by reduction in drug dosage. Patients in bed suffer less severe attacks than those who are active. Onset of severe headache in patients on MAO inhibitors may be associated with a temporary fall in blood pressure, which precedes the sharp rise found subsequently. It may be that the subsequent rise is a secondary response.

Addenbrooke's Hospital
Cambridge, England

See also: 795, 809, 821, 824, 862, 881, 882, 886, 903, 907, 909, 910, 913

BEHAVIORAL STUDIES

958 Leary, Timothy, Litwin, George H., & Metzner, Ralph. **Reactions to psilocybin administered in a supportive environment.** Journal of Nervous and Mental Disease, 137(6):561-573, 1963.

A naturalistic study of some of the ways consciousness may be altered by the plant derivative psilocybin was evaluated by questionnaire responses from 98 interested volunteers, 73 men and 25 women (mean age, 29.5 years), of varying backgrounds. The drug was given to groups of subjects in comfortable home surroundings, and the experiments were conducted by an experienced investigator. The setting was descrived by 78% of the subjects as "supportive" to the experience. The mean dosage was 18.1 mg (0.26 mg/kg body weight). Mean time for major effects was hours, and mean time for minor effects was 16.8 hours. Seventy percent of the subjects reported pleasant or ecstactic experiences; 88% learned something or had insights; 62% reported that the experience changed their lives for the better; and 90% wanted to repeat the experience. Seventy-two percent of the subjects reported primarily interpersonal, as opposed to personal, experiences. These results are not wholly adequate in describing the experience and must be regarded as tentative and preliminary. Several factors---selection of subjects, preparation, setting, suggestibility, attitudes of experimenter, and personality---may have been influential. A comparison of first and second experiences was made with a subsample of 35 subjects. Data indicate that there were no systematic overall differences between the first and second experiences.

Harvard University
Cambridge, Massachusetts

959 Kelm, Harold, Jensen, S. E., & Ramsay, R. W. **The figural after-effect and lysergic acid diethylamide (LSD-25).** Journal of Nervous and Mental Disease, 137(6):557-560, 1963.

The purposes of this study were (1) to test the prediction that LSD-25 will decrease the magnitude of the figural aftereffect, and (2) to compare the effect of LSD-25 on the figural aftereffect with the aftereffect of acute schizophrenics. Ten male alcoholics (24 to 46 years of age) and 10 schizophrenics (18 to 56 years of age) were the subjects. Each alcoholic patient received 200 gamma LSD-25, which is a higher dosage than normal since alcoholics are relatively resistant to this drug. The testing procedure in all subjects was to line up two illuminated lines that were in a dark tunnel into which the subjects looked. Four control alignments were made before the inspection periods, and four were made at the end of the session. The difference between the mean control and the mean experimental alignments was a measure of the figural aftereffect. The results obtained confirmed the prediction that LSD-25 would decrease the magnitude of the figural aftereffect. In addition, there was also a negative aftereffect when measurements were made 30 second after inspection, which was similar to that reported previously in a group of acute schizophrenics. Subjects given LSD-25 did not differ significantly from the schizophrenic group at any of the test times except for the 60-second test period. In this test condition, only half of the LSD-25 subjects showed the negative effect, whereas it was apparent in all of the schizophrenic subjects. The figural aftereffect patterns in both groups were of the type that would be expected of individuals with a high level of generalized cortical inhibition.

Saskatchewan Hospital
Weyburn, Saskatchewan, Canada

960 Krus, Donald M., Wapner, Seymour, Freeman, Harry, & Casey, Thomas M. **Differential behavioral responsivity to LSD-25.** Archives of General Psychiatry, 8:557-563, 1963.

The purpose of this study was to determine whether chronic schizophrenics show less psychologic response to LSD-25 than do normal adults. Subjects were 24 normal volunteers and 24 chronic schizophrenics (mean age, 30 and 39 years, respectively), 12 males and 12 females comprising each group. Both groups were in the average IQ range. The groups performed tasks in 20 experimental situations

for testing basic sensory--motor, perceptual, and conceptual processes under double-blind conditions, using 75μg LSD-25 and placebo, orally administered. Half of each group received LSD-25 first followed by placebo, and the other halves received the opposite sequence. One week was interpolated between conditions, and testing was begun 2 hours after treatments. Significant LSD-25 effects were found in twice as many situations in the normals (12 of 20) as compared with schizophrenics (6 of 20)---this result tends to support the notion of schizophrenic "resistance to LSD-25." Two other findings, however, qualify this interpretation. First, the significant effects were produced by a subthreshold dosage (75μg) for schizophrenics, and under placebo conditions, schizophrenics showed greater impairment of performance than normals. Since LSD-25 introduces even greater impairment, the initial low level of performance by the schizophrenics would tend to make manifestations of further impairment by LSD-25 in this group very difficult. Therefore, that greater impairment was manifested in six situations in a stronger argument against the schizophrenic-resistance hypothesis. Second, the effect of 75μg LSD-25 was not found differentially greater in normals than in schizophrenics. In addition to these quantitative findings, however, the qualitative findings that in normals gross psychological effects were universally present and that in schizophrenics these effects were absent indicates schizophrenic resistance. Taking all findings into account, the notion of schizophrenic resistance as a broad generalization must be questioned. Suggestions concerning reformulation of the problem and the research strategy involved are made.

Clark University
Worcester, Massachusetts

961 Merlo, Alicia B. & Izquierdo, Ivan. **The action of inhibitors of catechol-O-methyl-transferase on the exploratory activity of mice.** (Letter) Journal of Pharmacy and Pharmacology, 15:629-630, 1963.

The author states in a Letter to the Editor that, to give further support to the hypothesis that an adrenergic mechanism in the brain is related to inhibition, an actograph was used to measure exploratory activity in 77 white mice (12 to 30 g in weight) before and after i.p. administration of two catechol-O-methyltransferase inhibitors---pyrogallol (3, 6, 12.5, 50, and 200 mg/kg) and 3,4-dihydroxyphenylacetamide (300 mg/kg). Controls were given water only. Actograph records were run for 10 minutes before and for 20 minutes after injections. Responses were evaluated as the number of mice showing definite suppression of activity at each drug dosage. Exploratory activity was suppressed in 9 out of 10 mice tested with 3,4-dihydroxyphenylacetamide. Exploratory activity with pyrogallol decreased linearly with increasing dosage until, at 200 mg/kg, almost 90% of the mice showed inhibition. Since both of these inhibitors of catechol-O-methyltransferase increase catecholamines in various encephalic structures, these data support the hypothesis of a central adrenergic mechanism related to inhibition.

University of Buenos-Aires
Buenos-Aires, Argentina

962 Bentler, P. M., O'Hara, John W., & Krasner, Leonard. **Hypnosis and placebo.** Psychological Reports, 12:153-154, 1963.

The relationship between placebo responsiveness and susceptibility to hypnosis was investigated. Nineteen female nursing students, aged 18 to 21, were tested for pain perception thresholds and pain tolerance. They were then given a placebo pill that was described as a powerful pain reliever, and their pain perception and tolerance were measured again. Change in scores were recorded for the two pain tests. These same subjects were then hypnotized---15 were hypnotized individually, and 4 were hypnotized in two groups of two following the Stanford Hypnotic Susceptibility Scale, or its group adaptation. There was no significant correlation between placebo responsiveness and hypnotic susceptibility.

Stanford University and V. A. Hospital
Palo Alto, California

963 Liberson, W. T., Kafka, A., Schwartz, E., & Gagnon, V. **Effects of chlordiazepoxide (Librium) on fixated behaviour in rats.** International Journal of Neuropharmacology, 2(1-2):67-78, 1963.

Chlordiazepoxide was studied in rats with regard to its action on fixated behavior, discriminative learning, and learning a new cue. For the fixation procedure, chlordiazepoxide was given i.p. in doses of 5, 10, and 15 mg/kg. For the discriminative learning and learning of a new cue procedure, dosage was 15 mg/kg i.p. The major effect of chlordiazepoxide was the marked reduction of decision time of rats. This effect occurred in

spite of the depressant and sedative effect of chlordiazepoxide on rat behavior, and was a function of the dosage. The decrease in decision time was not associated with any increase of errors in learned responses; the decrease persisted for some time after drug withdrawal. Chlordiazepoxide prevented development of fixation in some rats, but this was not a consistent finding. It seemed to prevent fixation by favoring a trial and error learning process. Results for chlordiazepoxide are compared with those obtained previously for chlorpromazine, reserpine, phenobarbital, meprobamate, and certain stimulating agents.

Veterans Administration Hospital
Hines, Illinois

964 Spector, S., Hirsch, C. W., & Brodie, B. B. **Association of behavioural effects of pargyline, a non-hydrazide MAO inhibitor with increase in brain norepinephrine.** International Journal of Neuropharmacology, 2(1-2):81-93, 1963.

Pargyline administered to rabbits in repeated doses caused a rise in brain 5HT and norepinephrine and a pronounced increase in reactivity to environmental change. On discontinuance of the drug, these effects disappeared when the norepinephrine decreased, although 5HT was still maximally elevated. MAO activity was determined from the disappearance of 5HT added to brain homogenate as described by Bogdanski et al. The monoamines were estimated fluorometrically, 5HT and norepinephrine by the method of Mead and Finger, dopamine as described by Costa et al, and norepinephrine in sympathetic ganglia by a microadaptation of Shore and Olin as described by Kuntzman et al. When pargyline was given to rabbits that were depleted of amine stores with reserpine, levels of free 5HT in the brain and dopamine in the caudate nucleus rose rapidly, became maximal within 1 hour, and remained constant for about 7 hours, with the animals still deeply sedated. Only in about 12 hours, when there was a small rise in norepinephrine, were the effects of reserpine counteracted. The results indicate that MAO plays a different role than O-methyltransferase and has the important role of regulating the norepinephrine content of nerve endings. Pargyline caused rapid elevation of brain levels of norepinephrine and excitation in mice and rats and caused a slow elevation of norepinephrine and excitation in rabbits; it did not elevate brain norepinephrine or cause excitation in dogs and cats. In all these species, it caused a marked rise in brain 5HT.

National Institutes of Health
Bethesda, Maryland

965 Ul'yanova, L. A. **Effect of thyroid extract and 6-methylthiouracil on the conditioned reflex activity of dogs with experimental neuroses.** Farmakologiya i Toksikologiya, 26(4):406-410, 1963.

Food-secretory conditioned reflexes were developed in two dogs, and experimental neuroses then were evoked by shock, and by overloading of the stimulation and inhibition processes. The effects of thyroid extract and 6-methylthiouracil on the function of the thyroid gland were tested one-half year after experimental neurosis was developed. Thyroid extract was administered at the rate of 0.01 g/kg over 46 days, and 6-methylthiouracil was administered in dosage of 0.1 g/kg over a period of 36 days. Thyroid extract was tested first, and 6-methylthiouracil was tested 3 months later. One dog had a very unbalanced nature, and the other had balanced nervous processes. It was relatively difficult to produce an experimental neurosis in the latter. Thyroid extract produced improvement of cortical dynamics. Administration of 6-methylthiouracil deepened neurosis in the unstable dog, whereas the opposite was obtained with the relatively stable dog. The neurosis in the stable dog increased thyroid activity with administration of 6-methylthiouracil. The action of thyroid extract depressed thyroid function in the unstable dog. The results of the experiments show that the change in conditioned reflex activity under the influence of thyroid extract and 6-methylthiouracil depends upon the initial functional state of the cerebral cortex.

Laboratory of Experimental Pathology
Sochi Institute of Resorts and Sanatoria,
U.S.S.R.

966 Slater, Philip E., Morimoto, Kiyo, & Hyde, Robert W. **The effects of LSD upon group interaction.** Archives of General Psychiatry, 8:564-571, 1963.

This study is an exploratory determination of the effect of the psychotic phenomena by LSD-25 on interactive behavior in small task-oriented groups in a laboratory. Twenty-four males, all college students, were formed into six groups of four men. Each group met twice---once in a control meeting under normal conditions, and once about 1-$\frac{1}{2}$ hours after receiving LSD-25 (dosage not given).

(Three groups had their control meeting first, and three groups had their control meeting last, in order to control the length of time the subjects had been together.) Under each condition, the subjects spent 40 minutes on an intellectual group task and 10 minutes in informal social conversations. Under LSD-25, in the task session the ratio of questions to problem-solving attempts was higher, interaction was on a more concrete level, and negative affect was more inhibited. In the social session, subjects were more active and aggressive under LSD-25. In both sessions under LSD-25, interactions were more affectively toned (in a manic direction), and subjects addressed most of their remarks to the group as a whole. Subjects chosen as leaders under the drug were those who tried to cope with formal task demands and spent less time attempting to relieve internal tensions. Subjects under LSD-25 were less accurate in their perception of each others' attitudes toward themselves, partly because of a tendency to overestimate the neutrality of these attitudes. These findings suggest a preoccupation with the handling of inner tensions, and a consequent inability to respond to the feelings of others or to the task demands.

Massachusetts Mental Health Center
Boston, Massachusetts

967 Sheard, Michael H. **The influence of doctor's attitude on the patient's response to antidepressant medication.** Journal of Nervous and Mental Disease, 136(6):555-560, 1963.

This study was designed to ascertain if a more positive attitude by the doctor toward drug therapy, rather than a skeptical or negative attitude, is more often correlated with improvement in patients on antidepressants. Forty-six patients, 14 males and 32 females (20 to 70 years old), who were suffering from depression were treated with the following antidepressants: imipramine (50 mg t.i.d.), phenelzine (15 mg t.i.d.), and ibogaine (6.25 mg t.i.d.). The clinical changes were evaluated by a rating scale designed to measure depression, and were scored before and after 3 weeks of treatment. Twenty-five patients improved and 21 remained unimproved, as determined by this scale. Attitudes of 20 doctors toward the medication used in treating these patients were measured by a questionnaire and were scored quantitatively. A statistical analysis that compared the scores of doctors in the improved with those in the unimproved group showed a statistically significant difference ($p < 0.02$) between them. A warm, personal approach incorporating an optimistic belief in the possibility of relief, together with explanation, encouragement, and reassurance for side effects is an important vehicle for the drug used in the treatment of depression.

Yale University School of Medicine
New Haven, Connecticut

968 Klein, Donald F. & Fink, Max. **Behavioral reaction patterns with phenothiazines.** Archives of General Psychiatry, 7:449-459, 1962.

Eight groups of behavioral-change clusters (epitomizing dominant behavioral change patterns) were derived for 120 patients treated with the following phenothiazines: chlorpromazine (600 to 2,000 mg/day), prochlorperazine (30 to 90 mg/day), and promazine (600 to 1,000 mg/day). There were variations and fluctuations in dosage within groups, and changes from one drug to another were frequent. The patients were studied intensively by repeated interviews with patients, therapists, and ward personnel. The groupings were based on medication-response patterns, consisting of changes in symptoms, communication, affect, and social participation. These response patterns were found to be related to the pretreatment behavioral characteristics. The eight groupings follow, with the number of patients in each and their median age: suppressive denial (N 19, 25.0 years), reduction of anger (N 17, 35.0 years), affective stability (N 10, 19.0 years), autistic compliance (N 20, 19.5 years), decreased agitated depression (N 8, 30.0 years), somatization (N 17, 34.0 years), unaffected episodic agitation (N 11, 32.0 years), and unaffected episodic anxiety (N 8, 42.5 years). (A miscellaneous group contained 10 patients.) A description of the behavior in each group before and after treatment is given. The method and findings are discussed in relation to current psychopharmacological research, patient-population descriptions, medication effects, target symptoms, and mode of drug action.

Hillside Hospital
Glen Oaks, New York

969 Conners, C. Keith & Eisenberg, Leon. **The effects of methylphenidate on symptomatology and learning in disturbed children.** American Journal of Psychiatry, 120:458-464, 1963.

This is a controlled study of the psychopharmacologic actions of the stimulant methylphenidate, used to treat behavior disorders in children, and reported effective in previous clinical trials. Eighty-one (53 boys and 28 girls, from 7 to 15 years of age) emotionally disturbed children from two residential-care institutions, none diagnosed as brain-damaged, defective, or overtly psychotic, were treated on a double-blind basis for 10 days with 10 mg of methylphenidate t.i.d. and placebo. The dosage of drug was increased to 30 mg t.i.d. for the last 5 days. Symptom ratings by house parents and child-care workers were obtained before treatment and on the last day of treatment. Total symptom scores were improved in the drug group at a statistically significant level. The only adverse side effect was a high report (70%) of appetite loss in the drug group. Objective measures of learning and maze performance also showed reliable improvement in the drug group, minimizing the possibility that symptom changes were due to rater biases. The results agree with previous clinical studies and are interpreted as reflecting an activation of inhibitory controlling systems. A lengthy comment on this study follows the report proper.

Johns Hopkins University
School of Medicine
Baltimore, Maryland

970 Cheek, Frances E. **Exploratory study of drugs and social interaction.** Archives of General Psychiatry, 9:566-574, 1963.

The Bales Interaction Process Analysis technique was evaluated as to its feasibility for use in measuring alterations in individual and group behaviors in a four-person, continuing-discussion group that received varying doses of LSD-25. Four reformatory inmates, aged 23 to 25 years, participated in 24 total sessions. The design of the drug administration was as follows: no drug, then placebo, and then, sequentially, doses of LSD-25 p.o., ranging from 25µg to 100µg. Doses were increased by 25µg/week, and the study lasted about 4 weeks. At times, only one group member received the drug, and later all four individuals received the drug at the same time. Placebo sessions were interspersed throughout the series. After the 16th session, one subject was returned to the reformatory, and the sessions continued with three members. A task was presented to the group, usually the solution of a human-relations problem, that was to be accomplished in a set time period. The discussions were recorded, transcribed, and coded with a 20-category version of the Bales Interaction Categories. Highly significant behavioral changes were associated with the drug, and these changes confirmed literature reports. Total interaction rates, signs of tension, tension release, overt hostility, and disagreement rose markedly. In some cases, marked behavioral changes were picked up by the interaction technique, whereas, the subjective reports of the subjects regarding LSD-25 effects showed little change. These findings suggest that the Bales technique is worth further exploration, and that it shows potential for a clear and objective delineation of drug effects upon interpersonal behavior.

Bureau of Research in Neurology and
Psychiatry
Princeton, New Jersey

971 Izquierdo, Ivan & Merlo, Alicia B. **Effect of pyrogallol on acute learning in rats.** Journal of Pharmacy and Pharmacology, 15:154-155, 1963.

Pyrogallol was used to study the adrenergic mechanisms in learning in rats. In 26 rats, 19 of which received 200 mg pyrogallol i.p. and 7 of which received water 3 minutes before testing, the drug promoted habituation of investigatory-orienting and of arrest-unconditioned reflexes to a buzzer to which there normally was none. The buzzer lasted 3 seconds and was presented 50 consecutive times at intervals of 30 to 90 seconds. In other groups of rats, after 20 control buzzers, the buzzer was paired with a shock that was given 1 to 2 seconds after the buzzer sound. Appearance of the conditioned reflex was significantly lower in nine pyrogallol rats than in seven water-treated rats. In eight rats in which the drug was given later, during the reinforcement stage, when the instrumental response was stabilized, performance was unaffected. In seven rats injected with the drug 3 minutes before beginning an extinction of the conditioned reflex, the extinction rate was significantly higher than in seven water-treated rats. Administration of phentolamine (10 mg/kg) i.p., which counteracts the increase in blood pressure produced by pyrogallol, had no effect on extinction, either alone or combined with pyrogallol. Atropine (1 mg/kg) i.p., which counteracts duodenal motility, increased extinction when given alone in a way similar to pyrogallol. Atropine had no effect on extinction when given with pyrogallol. None of the rats showed any motor disturbance or neurological symptoms.

Faculty of Pharmacy and Biochemistry
Buenos-Aires, Argentina

972 Honigfeld, Gilbert. **Effect of an hallucinogenic agent on verbal behavior.** Psychological Reports, 13:383-385, 1963.

This is a first attempt to apply Cloze analysis (mutilation of a printed message by deleting every fifth word) to study the effect of psilocybin on understandability. A 22-year-old male student volunteer was given 9 mg of the drug p.o. at 9:40 A.M. Seven spontaneous speech samples were obtained between 10:30 A.M. and 1:15 P.M. A panel of 22 students were the normal-language users, and they were given typescripts of the mutilated speech samples. Each member of the panel was given a different speech sample and was told to complete it. A score of 1.00 was perfect, and a score of 0.00 was totally incorrect. A baseline level of understandability was about 0.427; that is, the panel filled in correctly 40% of the deletions. Over a period of time, the drug effects on language were similar to the effects of cerebral depressants (i.e., alcohol) on other psychomotor skills. After an initial enhancing effect at 10:50 A.M., a rapid deterioration in communication occurred that lasted until 12:15 P.M., after which there was a rapid return to baseline levels. These studies support the usefulness of Cloze analysis to evaluate drug effects and psychopathology.

VA Central Neuropharmacological Research Laboratory
Perry Point, Maryland

973 Pollard, John C., Uhr, Leonard, & Jackson, C. Wesley. **Studies in sensory deprivation.** Archives of General Psychiatry, 8:435-454, 1963.

Three sensory deprivation experiments were run to answer the following questions: (1) What is the effect of a single repetition of the sensory-deprivation experience? (2) Do men and women behave differently from each other under sensory deprivation? (3) Will subjects respond differently if, before sensory deprivation, they receive a tranquilizer or a stimulant? (4) Do different effects result from limiting the field of vision by translucent goggles or by a large translucent dome? (5) What is the effect of altering the "set" by giving the subjects information about previous subjects' sensory-deprivation experiences? Data are given on all questions except drug effects. The apparatus and experimental procedure are described, and the behavioral tests and measurements used are listed. The following three experiments were run: (1) effects of 8 hours of sensory deprivation compared with a second (repeated) 8 hours; (2) a comparison between using translucent goggles and a translucent semicylindrical dome to limit visual field; and (3) effects of suggestion on sensory-deprivation behavior.

University of Michigan
Ann Arbor, Michigan

974 Mata, Fernando. **Effect of dextro-amphetamine on bitter taste threshold.** Journal of Neuropsychiatry, 4(5):315-320, 1963.

A study was made on the bitter-taste threshold for quinine hydrochloride when varying amounts of d-amphetamine sulfate are administered. Thirty-two psychiatric inpatients, aged 14 to 57, were tested. Bitter-taste thresholds were determined by applying drops of quinine HCl solutions, in concentrations from 0.075 gm/100 ml tap water (0.0020782 M) to pure tap water, to the posterior area of the dorsal surface of the tongue. After the taste threshold was elicited, the subjects were given oral doses of d-amphetamine sulfate, 5, 10, or 15 mg, according to a randomized system with which they were classed into three groups. They were retested 1 hour later; the procedure was repeated the second and fourth days. Subjective experiences included lightheadedness, slight dizziness, and tiredness; in a few subjects, elevation of mood was also reported. A dose of 5 mg d-amphetamine did not affect the bitter-taste threshold, but 10 mg showed a decided trend toward lowering the threshold; 15 mg lowered the threshold, raising the sensitivity, at the 6% level of confidence.

Columbus State Hospital
Columbus, Ohio

975 Corson, Samuel A., Corson, Elizabeth O'Leary, & England, J. M. **The influence of meprobamate on conditioned and unconditioned visceral and motor defense responses.** In: Psychopharmacological Methods. New York, Pergamon Press, 1963, p. 244-255.

The influence of meprobamate, which decreases functional activity in the thalamus, on conditioned and unconditioned visceral and motor-defense responses was studied in dogs. Classic conditioned-reflex experiments were performed on dogs receiving 20 to 60 mg/kg meprobamate orally. Results are given for the influence of meprobamate on the following: (1) pain-conditioned antidiuretic responses; (2) paradoxical inhibition of un-

conditioned diuretic responses and on the development of conditioned diuretic responses; (3) conditioned electrolyte-retention responses; and (4) conditioned and unconditioned motor-defense responses. At the doses used, conditioned and unconditioned antidiuretic and electrolyte-retention responses were markedly decreased or abolished. The drug abolished neurotic reactions that manifested themselves as anorexia, adipsia, and antidiuretic and electrolyte-retention responses to a water load. Under meprobamate, it was possible to develop conditioned diuretic responses. The drug exerted no inhibitory effects on conditioned and unconditioned motor-defense responses or on specifically directed aggressive behavior.

Ohio State University Health Center
Columbus, Ohio

976 Stančák, A. **Krivka pracovnej výkonnosti v Bourdonovej skúške pod vplyvom alkoholu a Dexfenmetrazínu. (The effect of alcohol and dexphenmetrazine on the performance efficiency curve in Bourdon's test.)** Activitas Nervosa Superior, 5:189-190, 1963.

A group of 80 soldiers, 19 to 20 years old, was divided into four groups of 20 each, and given the Bourdon test following preprandial dexphenmetrazine and/or vodka. Group A (control) was given no test substance. Group B was tested 25 minutes after receiving 20 mg dexphenmetrazine, p.o. Group C received 210 ml 42% alcohol (in the form of vodka), and 65 minutes later was given 20 mg dexphenmetrazine, p.o. The test was administered 90 minutes after ingestion of the alcohol in this group. Group D was tested 90 minutes after ingestion of 210 ml alcohol. Two members each of Groups C and D did not finish the experiment. Alcohol produced significant effect on average performance results, including the groups given dexphenmetrazine. From these data, it may be concluded that dexphenmetrazine produces an insignificant increase in efficiency of test performance. This agrees with previous observations with phenmetrazine. Although dexphenmetrazine removes fatigue caused by alcohol, it produces pathological damage to the concentration of attention, as shown by a highly significant increase in errors.

Psychiatric Clinic, UPJŠ
Košice, Czechoslovakia

PHARMACOLOGY

977 Paris, R. **Sur l'action "tranquillisante" de quelques plantes médicinales.** (The "tranquilizing" action of several medicinal plants.) Annales Pharmaceutiques Francaises, 21:389-397, 1963.

Several plants with reputed tranquilizing or depressive effects were subjected to some of the methods used for classification of synthetic tranquilizers. Evaluation of drug effect was based on the activograph of Krauthammer, consisting of a mouse placed in a small cage suspended by a spring. The movements imparted to the cage by the mouse are registered by a photoelectric apparatus. Mice producing approximately 200 movements during the first 5 minutes were selected for test and control purposes. The test mice were administered 5 g/kg of plant extract s.c., and the control mice were given 5 g/kg physiological solution s.c. In addition to Rauwolfia serpentina, R. vomitoria, and R. macrophylla, which have known physiological effect, the following plants were found to have definite tranquilizing or depressive effect: poppy flower (Papaver rhoeas), passion flower (Passiflora incarnata), lime blossom (Tilia sylvestris, T. platyphylla, and T. argentea), orange blossoms (Citrus aurantium), valerian (Valeriana officinalis and Centranthus ruber), and Voacanga africana stem bark. No significant variation in movements was produced by the following: kawa-kawa root (Piper methysticum), plane-tree leaves, Avignon seed (Rhamnus infectoria), and Ambrevade leaves (Cajanus indicus).

Faculte' de Pharmacie de Paris
Paris, France

978 Stewart, Jane, Charest, Marie-Paule, & Herr, Ferenc. **A pharmacological investigation of potential antidepressants of the amitriptyline-type.** Journal of Medicinal Chemistry, 6(3):338-339, 1963.

The central and peripheral activities of a series of potential antidepressants were investigated. The compounds studied were dibenzo[a,d]-cycloheptadiene and dibenzo[a,d]-cycloheptatriene derivatives with the same side chains that have been applied in the phenothiazine, thioxanthene, and iminodibenzyl series. The compounds were tested for acute toxicity, effect on rectal body temperature, effect on maximal electroshock seizures, potentiation of a subhypnotic dose of alcohol, effect on a trained runway response, ataxic effect, and effect on a CAR. The mydriatic effect was also measured. The antispasmodic activity of the compounds in vitro was studied on isolated strips of guinea pig ileum using acetylcholine or histamine dihydrochloride. When the three main chemical classes (tertiary carbinols, olefins, and their corresponding saturated forms) were compared, the tertiary carbinols were the least potent both centrally and peripherally, whereas the corresponding olefins were generally the most potent. The introduction of a double bond in the 10-, 11-position of the ring caused an increase in central activity and a decrease in peripheral activity. Compounds in which the 3-position was substituted by chlorine had pharmacological properties more similar to chlorpromazine than to the antidepressants; a chlorine in the 3-position also depressed spontaneous motility at doses of 4 to 8 mg/kg i.p. Data for 47 compounds are given in tabular form.

Ayerst Research Laboratories
Montreal, Canada

979 Haydu, George G., Noreika, Leo, Sankar, D. Barbara, & Sankar, D. V. Siva. **Short-term effect of psychotropic drugs on platelets.** Archives of General Psychiatry, 9:510-512, 1963.

Four psychotropic drugs, chlorpromazine, chlorprothixene, imipramine, and tranylcypromine, were examined for effect on platelet count and platelet uptake of serotonin in 32 hospitalized psychotic cases. Chlorpromazine, chlorprothixene, and imipramine were given in doses of 50 mg t.i.d.; tranylcypromine was given in a dose of 10 mg t.i.d. Thrombocyte counts and uptake of radioactive serotonin by platelet-rich plasma were determined on all patients before drug administration and at 4-day intervals after the beginning of therapy. An increase in thrombocyte count occurred with all drugs, but the only statistically significant rise was with chlorprothixene. The thrombocytosis effect of the drugs functioned independently of

serotonin-uptake effect on platelets. Chlorpromazine treatment increased the relative uptake, but tranylcypromine decreased it; the rise with the other two drugs was not significant. The relationship of these effects is discussed.

Creedmoor State Hospital
Queens Village, New York

980 Stott, A. W. & Robinson, R. **Urinary phenols in patients treated with α-methyldopa.** (Letter) Journal of Pharmacy and Pharmacology, 15:773-774, 1963.

The urinary excretion of the metadrenalines and the phenolic acids 4-hydroxy-3-methoxymandelic acid (HMMA) and homovanillic acid (HVA) was measured following the administration of α-methyldopa. Hypertensive patients were fasted overnight, and a 2-hour control sample of urine was collected. After an oral dose of dl-α-methyldopa (usually 250 mg), no food was allowed for a further 4 hours. Urine samples were collected over successive 2-hour periods for 8 to 12 hours. Phenolic acids were extracted and separated by two-dimensional chromatography. The metanephrines were isolated, separated chromatographically, and estimated spectrophotometrically after their oxidation to vanillin. Two hours after methyldopa administration, the HVA excretion had fallen to 50% of that in the control period. Two hours later, it could hardly be detected on the chromatogram, and 4 hours later, HVA was undetectable. During the same period, there was a slight rise in the excretion of HMMA and a significant rise in the excretion of the metadrenalines. There was also a striking increase in excretion of vanillic acid during these studies---8 hours after methyldopa, 10 times the amount excreted in control periods was collected. About 10 to 12 hours after the dose of methyldopa, a compound appeared in the urine that was tentatively identified as α-methylnormetanephrine.

Group Pathological Laboratory
Warwick, England

981 Mawji, Sultan & Lockett, Mary F. **Pressor effects of adrenaline, noradrenaline and reflex vasoconstriction sensitised by low concentration of ganglion blocking drugs.** Journal of Pharmacy and Pharmacology, 15:45-55, 1963.

The potentiating effects of the ganglionic blocking agents, hexamethonium, tetraethylammonium, and pentolinium in low concentrations on the pressor effects of adrenaline, noradrenaline, and reflex vasoconstriction, were studied in cats, rats, and pigeons. Experiments were performed to measure: (1) the effect of ganglionic blocking agents on pressor responses to adrenaline and noradrenaline; (2) the effect of small repeated doses of ganglionic blocking agents on adrenal medullary amines in rats; and (3) the effect of ganglionic blocking agents on the uptake of noradrenaline by the adrenal glands and aortae of rats. In all cases, doses of blocking agents were too low to influence transmission in autonomic ganglia, but potentiated the pressor effects of adrenaline, noradrenaline, and reflex vasoconstrictions. The potentiation was not modified by spinalization or acute adrenalectomy; the potentiation was modified by pretreatment of an animal with reserpine (5 mg/kg 48 and 24 hours before experiments) and pretreatment of a tissue by postganglionic sympathetic denervation. The low concentrations of blocking agents used increase the uptake of noradrenaline by the adrenal medulla, increase total amine and the proportion of it present as adrenaline in the adrenal gland, fail to antagonize adrenal medullary depletion of catecholamine by reserpine, and can reverse a preexisting potentiation of the pressor effects of adrenaline and noradrenaline induced by cocaine.

Chelsea College of Science and Technology
London, SW.3, England

982 Ling, Alfred S. C. & Krantz, John C., Jr. **The effect of bis-(2,2,2-trifluoroethyl)ether on brain electrolytes and water distribution in the rat.** Biochemical Pharmacology, 12:394-395, 1963.

To study the effect of bis-(2,2,2-trifluoroethyl)ether (BTE) on brain electrolytes (sodium and potassium) and on water distribution, male albino rats (150 to 200 g) were convulsed with BTE (0.5 ml in a 3.4-liter chamber). During the convulsion, each rat was decapitated and the brain was removed. Blood samples were collected for serum-electrolyte determinations. The brains were dried to constant weight and the content of brain water was determined. Each whole brain was homogenized in deionized distilled water, deproteinized with 10% trichloroacetic acid, and diluted with deionized distilled water. After centrifugation, supernatant samples of the brain preparation were analyzed for sodium and potassium by flame photometry. Results showed a significant decrease in brain potassium and a significant increase in serum potassium during BTE-induced convulsions. A

significant increase in brain sodium during the convulsion was not accompanied by changes in serum sodium or brain-water content.

University of Maryland
Baltimore, Maryland

983 Kato, R., Nakamura, Y., & Chiesara, E. **Enhanced phenobarbital induction of liver microsomal drug-metabolizing enzymes in mice infected with murine hepatitus virus.** Biochemical Pharmacology, 12:365-370, 1963.

The effect of murine hepatitis virus of the Buescher strain (MHVB) on the liver microsomal drug-metabolizing enzymes of 17-day-old female mice (white Swiss strain) was investigated alone and in combination with phenobarbital pretreatment. A stock emulsion was prepared from the livers of infected mice. Mice treated with 0.2 mg i.p. of emulsion were sacrificed periodically from 6 hours to 4 days later. The percentage of mortality in infected mice at 48, 60, 72, and 96 hours was 7, 23, 40, and 62, respectively. Phenobarbital (80 mg/kg) was given s.c. 36 or 48 hours before excision. Mice were killed by decapitation and the pooled livers were homogenized in three parts (weight/volume) or isotonic potassium chloride. The nuclei and mitochondria were sedimented by centrifugation. In all groups of mice (virus-infected, treated with phenobarbital, and controls), the activity of the enzymes was determined by measuring the amount of hexobarbital, strychnine, or pentobarbital metabolized by a liver microsomal preparation during an incubation period of 1 hour. A diphasic effect of the infection with MHVB was observed: the enzyme activity was significantly increased 12 hours after the infection and was markedly depressed 48 to 60 hours after. Thirty-six hours after phenobarbital pretreatment, the enzyme activity was increased by 72%; in mice previously infected with MHVB, phenobarbital caused an increase of 93%. The protein content and overall RNA was decreased in livers of infected mice, but phenobarbital partially reversed the trend.

University of Milan
Milan, Italy

984 Kato, R., Vassanelli, P., & Chiesara, E. **A new potent inhibitor of microsomal drug-metabolizing enzymes 2:4-dichloro-6-phenylphenoxyethylamine hydrochloride (DPEA) (Lilly 32391).** Biochemical Pharmacology, 12:353-356, 1963.

The inhibitory action of 2,4-dichloro-6-phenylphenoxyethylamine hydrochloride (DPEA) on the metabolism of hexobarbital, pentobarbital, meprobamate, and carisoprodol was compared with that of β-diethylaminoethyl diphenylpropylacetate hydrochloride (SKF 525-A) and 2,4-dichloro-6-phenylphenoxy-N,N-diethylethylamine hydrobromide (Lilly 18947). Male and female Sprague--Dawley rats were used in all experiments. In vivo metabolism was determined by measuring drug concentrations in brain and serum 1 or 3 hours after drug administration. In vitro metabolism was determined by estimating the amount of the drugs in the liver microsomal preparation after an incubation of 1 hour. All injections were i.p. Final concentrations of hexobarbital, pentobarbital, meprobamate, and carisoprodol were 4×10^{-4} M, 2×10^{-4} M, 3×10^{-4} M, and 3×10^{-4} M, respectively. Pentobarbital hypnosis and carisoprodol paralysis were determined by duration of loss of the righting reflex; strychnine effect was determined from convulsions and mortality. DPEA is somewhat more potent than SKF 525-A in inhibiting the in vitro metabolism of the drugs, and it is from 2 to 10 times more potent than Lilly 18947. Pentobarbital metabolism is markedly inhibited by DPEA. The inhibitory action of DPEA on the in vivo metabolism of the drugs is the same or somewhat weaker than that of SKF 525-A, but it is markedly more potent than that of Lilly 18947. The effect of SKF 525-A is greater than that of DPEA in prolonging pentobarbital hypnosis and carisoprodol paralysis. The effect of DPEA on strychnine toxicity is about the same as that of SKF 525-A.

National Heart Institute
Bethesda, Maryland

985 Kato, R., Vassanelli, P., & Chiesara, E. **Inhibition of some microsomal drug-metabolizing enzymes by inhibitors of cholesterol biosynthesis.** Biochemical Pharmacology, 12:349-351, 1963.

A possible inhibitory action of triparanol and benzmalacene on drug metabolism in liver microsomes was studied in male Sprague--Dawley rats. Drug metabolism in the microsomal preparation was performed according to the method of Kato et al. Triparanol was dissolved in propyleneglycol and diluted with water before being added to the incubation mixture. Sodium benzmalacene was dissolved in distilled water. It was found that triparanol and benzmalacene cause 50% inhibition of the activity of the microsomal drug-metabolizing enzymes at a concentration range of 1×10^{-4} M to 5×10^{-4} M, but they stimulate

the metabolism of hexobarbital, pentobarbital, meprobamate, carisoprodol, and strychnine 48 hours after their administration. These results suggest the presence of some similar process between drug metabolism and cholesterol biosynthesis in liver microsomes.

University of Milan
Milan, Italy

986 Rogers, Larry A., Dixon, Robert L., & Fouts, James R. **The effects of SKF 525-A on hepatic glycogen and rate of hepatic drug metabolism.** Biochemical Pharmacology, 12:341-348, 1963.

The level of hepatic glycogen and rates of certain drug metabolisms were studied after i.p. injection of SKF 525-A (β-diethylaminoethyl diphenylpropyl acetate hydrochloride) in adult male white Holtzman rats (200 to 250 g in weight). After the animals were sacrificed, a liver slice (0.2 to 0.6 g) was removed and placed in 30% potassium hydroxide solution. Hepatic glycogen levels were determined with a phenol-sulfuric acid method. The side-chain oxidation of hexobarbital and the o-dealkylation of codeine were the metabolic pathways studied. After a single dose of SKF 525-A (20 mg/kg and 40 mg/kg), the level of hepatic glycogen was depressed maximally at 8 to 12 hours and returned to control level at 24 to 48 hours. The rate of hepatic enzymic metabolism of hexobarbital and codeine was depressed maximally 1 hour after administration of SKF 525-A and returned to control values between 24 and 48 hours. When SKF 525-A was administered every 12 hours for 5 days, the return of glycogen level and rate of hexobarbital and codeine metabolism to control values occurred at the same time; the effects were reversible. Adrenal-demedullated Sprague--Dawley rats responded to SKF 525-A the same way as did normal rats. SKF 525-A also decreased glycogen in force-fed and in starved animals, whether they were adrenal-demedullated or not. Glycogen synthesis was inhibited only by the 10^{-3} M concentration of SKF 525-A; the assay of glycogen synthetase activity was not affected at any concentration. At concentrations up to 10^{-3} M, SKF 525-A did not interfere with the chemical determination of glycogen.

State University of Iowa
Iowa City, Iowa

987 Canal, N., Ferri, S., & Scamazzo, T. **Effect of reserpine on liver tyrosine-α-ketoglutarate transaminase in the rat.** Biochemical Pharmacology, 12:299-300, 1963.

The activity of reserpine on liver tyrosine-α-ketoglutarate transaminase (TKT) was studied in vivo in male white rats (200 to 250 g in weight). Reserpine was injected i.p. in doses of 0.5, 1, and 5 mg/kg; controls received an equivalent volume of saline. The TKT activity was determined in whole-liver homogenate by the method of Kenney. The enzymic activity was measured with or without added pyridoxal-5-phosphate. Reserpine increased the level of TKT maximally at a dose of 5 mg/kg, but a clear-cut response was observed at 1 mg/kg. The 0.5-mg/kg dose had no effect. At the 5-mg/kg dose level, high levels of TKT were observed after 72 hours; enzyme activity returned to normal after 4 days.

University of Milan
Milan, Italy

988 Raynaud, G. & Valette, G. **Action des dérivés de la phénothiazine et de l'-halopéridol sur la crise audiogéne de la souris. (Action of phenothiazine derivatives and of haloperidol on the audiogenic crisis of the mouse.)** Archives Internationales de Pharmacodynamie et de Therapie, 142:425-439, 1963.

Audiogenic crises were produced in a select strain of Swiss albino mice that are almost 100% sensitive to sound convulsions, exhibiting clonic-tonic nonfatal convulsions with an average latent period of 3 to 5 seconds. The sound stimulus was derived from an electronic sound generator producing a mixture of frequencies to reproduce a natural noise at approximately 90 decibels intensity. The loudspeaker was above the experimental cage, located in a sound-dampened room. Cage movements, sound stimuli, and passage of time were automatically recorded on the same tape. All drugs were dissolved in physiological solution, except haloperidol, which was taken directly from the ampule. The drugs were administered i.p. Most experiments were conducted 50 minutes after injection. Complete inhibition of audiogenic convulsions was produced by 40 to 80 mg/kg of either aminopromazine or alimemazine, 8 to 10 mg/kg chlorpromazine or methopromazine, and 5 mg/kg levopromazine. Thioproperazine and prochlorperazine aggravated the course of convulsions in doses on the order of 10 mg/kg. Haloperidol also aggravates convulsions, with optimum activity obtained at doses of 2.5 mg/kg.

Universite de Paris
Paris, France

989 Nieschulz, Von O. **Über Schwimmversuche mit Mäusen. (Swimming tests with mice.)** Medicina Experimentalis, 8:135-140, 1963.

Endurance tests were run with mice rather than rats to see if the smaller laboratory animals could be used to assay the effect of psychopharmacological drugs on endurance. Mice were forced to swim in a round glass container 29 cm in diameter, containing water at 15° or 20° C, without artificial waves. Tonic cramp of the hind legs was taken as indication of exhaustion. The observers were unaware of the drug given to individual mice. Each mouse was tested only once. Swimming in water at 15° and 20° C produced a drop of 10° C in body temperature after 5 minutes, and a drop of 14° to 15° C at the point of exhaustion. Swimming endurance was greatly affected by this drop in body temperature. Controls for each test were run on the same day as the test. Drugs were given p.o. 1 hour before the test. Small doses of caffein had no, or only slight effect on swimming endurance. Methylaminodibenzylmethane (5 mg/kg) produced an increase of 44% in endurance at a water temperature of 15° C, and a 21% increase at 20° C. Imipramine (5 and 10 mg/kg) prolonged endurance at 15° C, but had less effect at 20° C. Higher doses were ineffective, or decreased endurance. Amphetamine (1 mg/kg) had no effect at 15° or 20° C, and higher dosage (5 mg/kg) shortened endurance. Meprobamate (100 to 200 mg/kg) shortened endurance at both temperatures. Chlorpromazine (10 mg/kg) also definitely limited endurance. This test design offers a relatively rapid assay of dose range, including assay of limitation of physical endurance and of most undesirable side effects.

Promonta Company
Hamburg, Germany

990 Strömme, Johan H. **Inhibition of hexokinase by disulfiram and diethyldithiocarbamate.** Biochemical Pharmacology, 12:157-166, 1963.

The activity of hexokinase was evaluated by measuring the generation of reduced triphosphopyridine nucleotide (TPNH) as the glucose-6-phosphate formed in the hexokinase reaction was enzymatically oxidized to 6-phosphogluconate. The increase in TPNH was followed continuously in a recording spectrophotometer at 340 mμ and 37° C for 6 to 10 minutes. The enzyme-inhibitory effect of disulfiram and of diethyldithiocarbamate was tested by preincubating either a brain or yeast hexokinase suspension in the presence of these compounds. Hexokinase activity was measured immediately after the addition of the compounds to be tested and at suitable time intervals during the incubation. Disulfiram was found to be a potent inhibitor of hexokinase. Diethyldithiocarbamate inhibited the enzyme only when it was oxidized to disulfiram, which was done by adding oxidized cytochrome c to the system. Reduced glutathione prevented the inhibition. Complete reactivation was obtained with small concentrations of cysteamine, indicating that inhibition is due to a blocking of essential ——SH groups on hexokinase. Results are discussed in relation to the therapeutic use of disulfiram.

University of Oslo
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991 Pscheidt, Gordon R. & Himwich, Harold E. **Reserpine, monoamine oxidase inhibitors, and distribution of biogenic amines in monkey brain.** Biochemical Pharmacology, 12:65-71, 1963.

Twenty-one Macacus rhesus monkeys (3.3 to 8.0 kg in weight) were given reserpine and MAO inhibitors, both singly and in combination, and the levels of serotonin and norepinephrine were determined in various brain regions. Five monkeys served as controls; the remaining animals, in groups of two or three, received the following drugs: nialamide (25 mg/kg), isocarboxazid (2 or 20 mg/kg), reserpine (1 mg/kg), reserpine and nialamide, and reserpine and isocarboxazid. All drugs were injected i.m. once a day for 6 days, and the animals were sacrificed on the seventh day. The animals were anesthetized with pentobarbital, the carotid arteries were cannulated, and the head was perfused with 300 to 500 ml of saline prior to removing the brain. The distributional pattern of these amines in monkey brain was similar to that described for other mammals. This primate species resembles rodents, not cats and dogs, in its biochemical response to MAO inhibitors; i.e., nialamide and isocarboxazid increased brain levels of both serotonin and norepinephrine. The greatest amounts were found in the midbrain-hypothalamus, thalamus, and pons-medulla. Continued administration of reserpine reduced the brain levels of both amines to low values in all areas, except for one high norepinephrine value in the thalamus. Both nialamide and isocarboxazid elevated brain levels of serotonin and norepinephrine in nearly all brain regions. The combination of reserpine and isocarboxazid resulted in lower levels of brain amines than when the inhibitor was given above. The combination of reserpine and nialamide resulted in higher brain serotonin levels than when only nialamide was adminis-

tered. Therefore, in this study, nialamide exerted more than the single action of inhibition of MAO.

Galesburg State Research Hospital
Galesburg, Illinois

992 Freeman, A. R. & Spirtes, M. A. **Effects of chlorpromazine on biological membranes——II. Chlorpromazine-induced changes in human erythrocytes.** Biochemical Pharmacology, 12:47-53, 1963.

Different techniques were used to study the effect of chlorpromazine on the permeability of human erythrocytes to various compounds. In addition to controls, chlorpromazine sulfoxide (a weak tranquilizer) and trifluoperazine were also compared. To measure the effect of chlorpromazine on the hemolysis time of human erythrocytes, a photometric method was used. Control values were obtained by recording hemolysis time in 0.3 M urea or 0.3 M glycerol alone; then, 1×10^{-3} to 1×10^{-5} M chlorpromazine was added to each test solution. Total hemolysis time was retarded in both the urea and glycerol systems in concentrations as low as 5×10^{-4} and 10^{-5} M chlorpromazine, respectively. In a comparison of the drug with its sulfoxide on the turbidity of a suspension of erythrocytes in 0.5% NaCl, spectrophotometric measurements showed that the suspension had greater turbidity in the presence of chlorpromazine than in its absence. This effect was significant at 10^{-5} M, whereas the sulfoxide was inactive even at 10^{-4} M. In protecting human red blood cells against hypotonic hemolysis, chlorpromazine and trifluoperazine were active at 7.5×10^{-6} and 10^{-6} M, respectively, as measured spectrophotometrically. Chlorpromazine sulfoxide was ineffective even at 10^{-3} M. In the last test, in which drug uptake by erythrocyte suspensions in isotonic NaCl was also measured spectrophotometrically, approximately twice as much trifluoperazine is taken up by the cells as chlorpromazine; very limited absorption of the sulfoxide takes place in the same 15-minute period. The concentration of all three drugs was 2.5×10^{-5} M. These effects correlated with the clinical potency of the compounds and varied directly with the amounts of each drug absorbed by the erythrocytes.

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993 Spirtes, M. A. & Guth, P. S. **Effects of chlorpromazine on biological membranes——I. Chlorpromazine-induced changes in liver mitochondria.** Biochemical Pharmacology, 12:37-46, 1963.

The effects of chlorpromazine on mitochondrial permeability were studied. The swelling of rat liver mitochondria suspended in isotonic sucrose at pH 7.4 was measured spectrophotometrically and by water and sucrose entry. At concentrations of 5×10^{-6} to 10^{-4} M, chlorpromazine inhibited this swelling. Higher concentrations also caused agglutination of the mitochondria suspended in either isotonic sucrose or potassium chloride. In the potassium chloride medium, chlorpromazine at 5×10^{-6} to 10^{-4} M did not inhibit swelling. Chlorpromazine sulfoxide had no effect on mitochondria suspended in either isotonic sucrose or potassium chloride.

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Philadelphia, Pennsylvania

994 Carver, Michael J. **Differential effects of phenothiazines on hexose phosphate dehydrogenases.** Biochemical Pharmacology, 12:19-24, 1963.

The inhibitory effects of various phenothiazine derivatives on glucose-6-phosphate dehydrogenase (G-6PD) and 6-phosphogluconate dehydrogenase (6-PGD) from beef adrenal cortex and rat brain were compared. The enzymes were prepared according to the method of Kelly et al. Assays for G-6PD were based on the method of Kornberg and Horecker; assays for 6-PGD were based on the method of Horecker and Smyrniotis. The six phenothiazine derivatives (thioproperazine, promazine, trimeprazine, methoxypromazine, promethazine, and acetophenazine) were selected on the basis of their solubility in glycylglycine buffer, pH 7.4. The phenothiazines inhibited both G-6PD and 6-PGD from beef adrenal cortex and G-6PD from rat brain tissue. With the adrenal enzyme, competitive inhibition of G-PGD was noted with thioproperazine; however, no inhibition of the rat brain enzyme could be obtained with a wide variety of phenothiazines. Imipramine inhibition of G-6PD from bovine adrenal and rat brain was comparable to promethazine inhibition. No effect was observed on 6-PGD.

Nebraska Psychiatric Institute
Omaha, Nebraska

995 Witter, Robert F. & Gaines, Thomas B. **Relationship between depression of brain or plasma cholinesterase and paralysis in chickens caused by certain organic phosphorus compounds.** Biochemical Pharmacology, 12:1377-1386, 1963.

A study was made of the relationship between the inhibition of plasma or brain cholinesterase in chickens and the paralytic syndromes caused by DFP (diisopropyl fluorophosphonate), TOCP (triorthocresol phosphate), malathion, ronnel, EPN (0-ethyl 0-p-Nitrophenyl phenylphosphonothioate), and 0,0-diethyl p-chlorophenylmercaptomethyl dithiophosphate (Trithion). DDVP (0,0-dimethyl 2,2-dichlorovinyl phosphate) and dimethyl (2,2,2-trichloro-1-hydroxyethyl) phosphonate (Dipterex) served as nonparalytic controls. TOCP was the only compound tested that was a specific inhibitor of brain cholinesterase. The chickens used in the tests were females of a sex-linked strain and weighed 2.5 to 3.0 kg. They were dosed s.c. on the right side, between the thigh and the wing, with the organic phosphorus compound in peanut oil. Dipterex was given as an aqueous solution. Chickens were pretreated with 15 mg/kg atropine p.o. to minimize the acute effects of the toxicant. All compounds except EPN inhibited plasma cholinesterase. All compounds tested inhibited brain pseudocholinesterase and/or true cholinesterase, and all paralytic compounds tested except DFP produced a prolonged inhibition of brain pseudocholinesterase and/or true cholinesterase, which lasted for 5 to 17 days. There appears to be no causative relationship between the prolonged inhibition of brain cholinesterase and the paralytic syndromes.

Communicable Disease Center
Atlanta, Georgia

996 Datta, R. K. & Ghosh, J. J. **Action of isoniazid and nialamide on brain cortex ribosomes.** Biochemical Pharmacology, 12:1355-1362, 1963.

The action of the antidepressants isoniazid and nialamide on the ribosomal particles of goat brain cortex tissue has been studied. Brain cortex slices from freshly slaughtered goats were suspended in a glucose-buffer solution and were incubated for 2 hours at 37° C with either drug (1 mg/g wet tissue). Untreated slices were suspended with glucose-buffer only. The ribosomes were prepared from the slices, and then RNA was extracted from them. Chemical estimations (nitrogen, phosphorus, protein, nucleotides, and acid-soluble nucleotides) and enzymic estimations (ribonuclease, phosphomonoesterase, and phosphodiesterase) were made. The drugs do not affect the chemical and nucleotide compositions or the ultraviolet-absorption characteristics of the ribosomal particles. During the action of the drugs, however, the ribosomal particles are made very unstable and become more susceptible to breakdown, releasing protein, RNA, and acid-soluble nucleotides into the media. This results in the loss of ribosomal enzyme activity. To see if this significant loss in enzyme activity was caused by the direct action of these drugs, fresh ribosomes were incubated with the drugs. Little inhibition of enzyme activity was observed here, although with nialamide the inhibition was greater. Apparently, these drugs have acted indirectly, by changing the natural environmental conditions (i.e., pH, ionic concentrations, etc.).

University Colleges of Science and Technology
Calcutta -9, India

997 Moore, K. E. & Lariviere, E. W. **Effects of d-amphetamine and restraint on the content of norepinephrine and dopamine in rat brain.** Biochemical Pharmacology, 12:1283-1288, 1963.

Since animal responses to amphetamine are influenced by environment, the effects of stressful situations, in addition to aggregation, were examined. Female Sprague--Dawley rats (180 to 220 g in weight) were injected i.p. in a constant volume of 5 ml/kg d-amphetamine and placed in cages that prevented locomotion or posture changes. Periodically, animals were sacrificed by decapitation and their brains were removed, weighed, and homogenized in cold 0.4 N perchlorate. The tissue extracts and standards were purified on alumina-containing chromatographic columns according to the method of Moore and Brody. Norepinephrine was determined by a modification of the method of Bertler et al. and dopamine by a modification of the method of Carlsson and Waldeck. Four hours after the injection of 10 or 30 mg/kg amphetamine, the content of brain norepinephrine was significantly reduced; repletion occurred within 72 hours. The dopamine content was only reduced slightly in amphetamine-treated animals and was returned to control levels within 4 hours. Restraint did not enhance the amphetamine-induced release of norepinephrine.

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998 Freeman, A. R. & Spirtes, M. A. **Further effects of chlorpromazine on the human erythrocyte membrane.** Biochemical Pharmacology, 12:1235-1237, 1963.

This work intended to implicate passive osmotic permeability in the mechanism of action of phenothiazines. Erythrocytes were exposed to hypotonic saline, and after centrifugation, the supernatants were removed and analyzed for the percentage of hemolyzed cells according to the method of Freeman and Spirtes. The remaining erythrocytes were analyzed for intracellular ions by a modification of the method of Post and Jolly. Analyses were performed on erythrocytes in the presence and absence of 2.5×10^{-5} M chlorpromazine, on erythrocytes suspended in isotonic sodium chloride solution, and in a hypotonic sodium chloride solution resulting in 30% hemolysis. Chlorpromazine (2.5×10^{-5} M) brought the 30% control hemolysis down to 12%. Compared to normal cells, the erythrocytes remaining after the hypotonic treatment gained in sodium content and lost in potassium content, the ratio of gain to loss being 1:1. Chlorpromazine inhibited passive ionic leakage in both directions without disturbing the ratio of the ion exchange. Chlorpromazine probably inhibits the passive movement of water and ions in erythrocytes exposed to hypotonic stress. The ability of the drug to alter water movement appears not to be related to its action on the leakage of ions.

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999 Sellinger, O. Z. & Weiler, P., Jr. **The nature of the inhibition in vitro of cerebral glutamine synthetase by the convulsant, methionine sulfoximine.** Biochemical Pharmacology, 12:989-1000, 1963.

The effect of dl-methionine-dl-sulfoximine (MSO) on particulate and soluble preparations of glutamine synthetase from the rat cerebral cortex was investigated. Male Holtzman rats (150 to 200 g in weight) were decapitated, their brains were exposed, and the cortical layers were removed. After treatment, the supernatant fluid, representing the soluble cell material, contained about 50 mg of tissue equivalent per milliliter. Results showed that the activity of glutamine synthetase in particulate form always exceeded that of the enzyme in soluble form. MSO inhibition of the enzyme in both forms was found to be the same. Preincubation with MSO failed to affect the extent of inhibition, but with ATP, some protection toward inhibition was afforded. Other compounds structurally related to l-glutamate, such as l-methionine, failed to alleviate the inhibition.

Tulane University School of Medicine
New Orleans, Louisiana

1000 Peng, C. H. Lee & Walsh, E. O'F. **Effects of morphine on the hormonal control of metabolism. I. In vitro effects of morphine and hydrocortisone on utilization of glucose by muscle of normal and chronically morphinised rats.** Biochemical Pharmacology, 12:921-930, 1963.

Female albino rats (140 to 180 g in weight) that had been maintained on a standard diet were fasted 24 hours, and then decapitated prior to excision of the diaphragm. Chronically morphinized rats had received daily injections of 1% morphine sulfate (30 mg/kg) for 5 to 6 weeks. Control rats received saline injections for the same period. Glucose was determined by the method of Nelson after deproteinization of the sample with barium hydroxide and zinc sulfate. Glycogen was determined by conversion to glucose according to Good et al. Lactate was measured by the method of Barker and Summerson after deproteinization of the sample with trichloroacetic acid. Results showed that morphine stimulated glycose uptake in normal tissue, but depressed glucose uptake and lactate production in chronically morphinized tissue. Hydrocortisone antagonized these effects of morphine; morphine antagonized the effect of hydrocortisone on respiration, but tended to enhance the effects of the hormone on glycogen metabolism. Diaphragm tissue from chronically morphinized animals had a higher glycogen content, but was no different from that of normal animals in basal metabolic activity.

University of Hong Kong
Hong Kong, China

1001 O'Neill, John J., Simon, Stuart H., & Cummins, Joseph T. **Inhibition of stimulated cerebral cortex respiration and glycolysis by cholinolytic drugs.** Biochemical Pharmacology, 12:809-820, 1963.

The selected inhibition of stimulated aerobic glycolysis and respiration in rat or guinea-pig cerebral cortex by six cholinolytic drugs is described. The following compounds were used: JB-840 (N-methyl-3-piperidylphenylcyclohexyl glycolate hydrochloride), JB-336 (N-methyl-3-piperidyl benzilate), JB-344 (N-methyl-3-piperidylphenyl-2-thienyl glycolate hydrochloride), JB-329 (N-ethyl-3-piperidylphenylcyclopentyl glycolate hydrochloride), JB-318 (N-ethyl-3-piperidyl benzilate hydrochloride), and Daricon (1-methyl-1,4,5,6-tetrahydro-2-pyrimidylmethylcyclohexylphenyl glycolate hydrochloride). After the male Wistar rats or male guinea pigs used in the experiments were killed by decapitation, the

brains were removed and dropped into cold Tris--Ringer-glucose saline, then divided into two cerebral hemispheres. Slices of brain tissue were obtained with a specially designed apparatus. All equipment and techniques are described in detail. The six drugs blocked stimulated respiration of rat and guinea-pig cerebral cortex (at concentrations from 5×10^{-4} to 5×10^{-5} M) without demonstrable effect on unstimulated tissue. The marked depression of stimulated respiration by JB-840 was accompanied by a significant decrease in the amount of glucose utilized and lactate produced. There were no significant effects on these parameters in unstimulated tissue.

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1002 Brossard, Maurice & Quastel, J. H. **Effects of morphine and Tofranil on the incorporation of phosphate (^{32}P) into phospholipids of rat brain slices.** Biochemical Pharmacology, 12:766-768, 1963.

The effects of morphine and imipramine (an antidepressant) on the labeling of phospholipids with inorganic P^{32} in slices of rat brain cortex were studied. Morphine was tested at concentrations of 2, 5, and 10 mM, and imipramine was tested at 0.05, 0.1, and 0.5 mM. At 5 and 10 mM, morphine did not affect the rate of oxygen uptake in brain-cortex slices, but did increase the labeling of phospholipids. At 0.05 and 0.1 mM, imipramine did not affect respiration, but did increase P^{32} uptake by 39% and 70%, respectively; at 0.5 mM, respiration and labeling of phospholipids were markedly inhibited. Brain phospholipids were fractionated by chromatography. Stimulation of P^{32} uptake was due mainly to increased P^{32} incorporation into phosphatidic acid, phosphoinositide, and to a lesser extent, into phosphatidyl serine. Neither drug affected labeling of phosphatidyl choline or phosphatidyl ethanolamine. The effects of morphine and imipramine are similar to those of acetylcholine and chlorpromazine.

McGill-Montreal General Hospital
Research Institute
Montreal, Canada

1003 Steinberg, Daniel, Vaughan, Martha, Nestel, Paul J., & Bergström, Sune. **Effects of prostaglandin E opposing those of catecholamines on blood pressure and on triglyceride breakdown in adipose tissue.** Biochemical Pharmacology, 12:764-766, 1963.

The effects of prostaglandin E_1 (PGE_1) on the release of glycerol from adipose tissues in the presence of lipolytic hormones and on the hypertensive action of epinephrine and norepinephrine were studied. Lipolytic hormones and PGE_1 were added to rat epididymal fat pads, and glycerol release from the fat pads was used as a measure of the rate of lipolysis. The release of flycerol was significantly reduced by PGE_1 (0.1μg/ml) in the presence of epinephrine (0.1μg/ml), norepinephrine (0.2μg/ml), ACTH (0.04 unit/ml), glucagon (5μg/ml), and thyroid-stimulating hormone (10μg/ml). Similar suppressive effects were produced by PGE_1 on free-fatty-acid release induced by the lipolytic hormones, but the action was less potent. The PGE_1 effects in the absence of these hormones were variable, but reduction in glycerol release was noted. The effect of PGE_1 alone and in combination with epinephrine or norepinephrine on the mean arterial pressure of intact mongrel dogs was studied. Using PGE_1 (6μg/kg to 12.5μg/kg) alone caused a profound drop in blood pressure; PGE_1 (5μg/kg to 12.5μg/kg) injected with epinephrine (2.5μg/kg to 5.0μg/kg) or norepinephrine (5.0μg/kg) reduced the catecholamine pressor response by about 52%.

National Heart Institute
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1004 Arnold, A., McAuliff, J. P., Sobell, S. D., & Archer, S. **Dose response effects on norepinephrine-depletion of reserpine and guanethidine in bretylium-pretreated rats.** Biochemical Pharmacology, 12:1231-1232, 1963.

Dose-response effects of reserpine and guanethidine on depletion of heart norepinephrine in bretylium-treated rats were studied. Adult female Sprague--Dawley rats were pretreated i.p. daily with 20 mg bretylium/kg for 2 days. After the fourth bretylium injection, rats were given i.p. doses of 0.0625, 0.25, or 1.0 mg/kg reserpine or 2, 8, or 32 mg/kg guanethidine. Control animals (not pretreated) received i.p. doses of 0.156, 0.625, or 2.5 mg reserpine or 0.156, 0.625, 2, or 8 mg/kg guanethidine. Reserpine exerted maximal effect in control animals at about 0.25 mg/kg. After bretylium pretreatment, about four times as much reserpine is required to achieve a comparable depletion of heart norepinephrine. Guanethidine exerted maximal effect in control animals at about 8 mg/kg. In bretylium-pretreated animals, about 32 mg/kg were necessary to get the same effect. With both drugs, a fourfold increase in dose was required to overcome the effects of bretylium. Previously reported conflict-

ing results on the effect of bretylium pretreatment on norepinephrine depletion by reserpine apparently resulted from differences in dosage employed.

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Rensselaer, New York

1005 Supek, Z., Urioć, B., & Rabadjija, M. **The effect of some nucleotoxic agents on urinary excretion of 5-hydroxyindolacetic acid in rats.** Biochemical Pharmacology, 12: 759-761, 1963.

Since X-irradiation increases urinary excretion of 5HIAA and nucleotoxic drugs show similarities with ionizing radiation, the effect of two nucleotoxic drugs, nitrogen mustard (a radiomimetic poison) and urethane (a spindle poison) on urinary excretion of 5HIAA was studied. For comparison, chloral hydrate, which is not a nucleotoxic drug, was also tested. Albino rats of both sexes weighing 150 to 250 g were used. Urine was collected 3 days before and 3 days after poisoning. Nitrogen mustard (3 mg/kg) was given i.p.; urethane (1,500 mg/kg) and chloral hydrate (500 mg/kg) were given s.c. Both nitrogen mustard and urethane produced significant increases in 5HIAA urinary excretion on the second day after injection. Chloral hydrate showed no such effect. Apparently, only the nucleotoxic drugs increase 5HIAA excretion, and there is no difference in effect of the two types of nucleotoxic drugs, radiomimetic or spindle poisons.

University of Zagreb
Zagreb, Yugoslavia

1006 Strömme, Johan H. **Effects of diethyldithiocarbamate and disulfiram on glucose metabolism and glutathione content of human erythrocytes.** Biochemical Pharmacology, 12:705-715, 1963.

The oxidation of diethyldithiocarbamate and the reduction of disulfiram (tetraethylthiuram disulfide) in intact human erythrocytes and the effects of these two agents on glucose metabolism and glutathione content in the blood cells were studied in vitro. At low concentrations of diethyldithiocarbamate, glucose consumption is stimulated, but, at higher concentrations, an inhibition of metabolism develops. The mechanism underlying this inhibition involves the oxidation of diethyldithiocarbamate to disulfiram, which in turn inhibits the hexokinase. Disulfiram interfers with other steps in carbohydrate metabolism, but high concentrations of the inhibitor are required. Methemoglobin serves as the immediate electron acceptor in the conversion of diethyldithiocarbamate to disulfiram. This pigment is continuously formed by a diethyldithiocarbamate-catalyzed autoxidation of hemoglobin. Evidence indicates that the glutahione-glutahione reductase system gives efficient protection against disulfiram poisoning of erythrocytes.

University of Oslo
Oslo, Norway

1007 Santi, R., Ferrari, M., & Toth, C. E. **Papaverine-like pharmacological properties of rotenone.** (Letter) Journal of Pharmacy and Pharmacology, 15:697-698, 1963.

To test the hypothesis that the spasmolytic effect of papaverine is related to the inhibition of oxidative phosphorylation, rotenone, which is biochemically similar to papaverine and the most selective inhibitor of oxidative phosphorylation known, was studied for papaverine-like activities (spasmolytic, vasodilator, and respiratory-stimulant effects). Spasmolytic activity was tested on isolated gut (guinea-pig ileum and rabbit duodenum). The vasodilator effect was measured on the hindlimb of the dog by recording arterial femoral flow with a Shipley--Wilson rotameter. Effects on respiration and arterial blood pressure were studied in rabbits and dogs. Rotenone, 10^{-8} to 10^{-9} M (w/v), mimics the spasmolytic effect of papaverine, but is 100 times more potent. When injected i.a., rotenone (15 to 20 mg) increases blood flow 70% to 80% for 120 to 150 seconds. The drug shows a respiratory-stimulant effect when injected i.a. (15μg/kg to 20μg/kg) or i.v. (15μg/kg to 25μg/kg). From the biochemical and pharmacodynamic similarities of rotenone and papaverine, it was assumed that papaverine's effects were related to the inhibition of oxidative phosphorylation.

University of Padua
Padua, Italy

1008 van Rossum, J. M. & Hurkmans, J. A. Th. M. **Reversal of the effect of α-methyldopa by monoamine oxidase inhibitors.** Journal of Pharmacy and Pharmacology, 15:493-499, 1963.

The reversal of the sedative effect of α-methyldopa by MAO inhibitors was studied in female mice of the R.Q. strain. A dose of 562μmoles/kg α-methyldopa was injected i.p. into: (1) two control-group mice; (2) two mice who had received 562μmoles/kg pargyline 2 hours previously; and (3) two mice that, in addition to pargyline, had received 100μmoles/kg N-(m-hydroxybenzyl)-N-methylhydrazine 30 minutes before α-methyldopa. Two more mice were pretreated with reserpine (1 mg/kg)i.p. for 3 to 4 days prior to treatment with 562μmoles/kg pargyline, followed 2 hours later by 562μmoles/kg α-methyldopa. In addition, dl-α-methyl-m-tyrosine (α-MMT) was studied alone in doses of 316μmoles/kg and 562μmoles/kg, and 2 hours after 562μmoles/kg pargyline in doses of 31.6μmoles/kg and 100μmoles/kg α-MMT. In mice pretreated with pargyline, the usual sedative effect α-methyldopa was revised, causing a prolonged increase in motor activity and control excitation, which appeared 2 to 3 hours after injection. The excitation is caused by accumulation of free catecholamines liberated by amines that are slowly formed by decarboxylation of α-methyldopa.

University of Nijmegen
Nijmegen, Netherlands

1009 Davey, M. J. & Farmer, J. B. **The mode of action of tyramine.** Journal of Pharmacy and Pharmacology, 15:178–182, 1963.

A study was made to determine whether the noradrenaline content of the isolated perfused guinea-pig heart and its perfusate, as well as the magnitude of the positive inotropic effect, are related to the total amount of tyramine given. Observations were also made with guanethidine, phenethylamine, amphetamine, bretylium, and ephedrine. Guinea-pig hearts were perfused by the method of Langendorff with a warm, oxygenated Kreb's solution; 100μg of the test amine was injected into a cannula close to the heart every 5 to 10 minutes until no positive inotropic effect was observed. A total of 3 mg tyramine was needed before the amine failed to produce a positive inotropic effect, but the response was much reduced after 1.5 mg. Decrease in the positive inotropic response was paralleled by a decrease in the noradrenaline content of the heart and a release of noradrenaline in the perfusate. When tyramine no longer produced an inotropic effect, further injections of tyramine did not produce any greater decrease in heart noradrenaline. Guanethidine and phenethylamine decreased heart noradrenaline; amphetamine produced no change, and ephedrine and bretylium increased heart-noradrenaline concentration.

Pfizer Limited
Sandwich, Kent, England

1010 Laverty, R. **A nervously-mediated action of angiotensin in anaesthetised rats.** Journal of Pharmacy and Pharmacology, 15:63–68, 1963.

Synthetic and naturally occurring angiotensin, previously assumed to have no action on the CNS, was tested in the isolated, innervated, perfused hindlimb of the rat for effect on peripheral blood vessels; small doses of noradrenaline were also tested. The experimental animals were prepared so that drugs could exert an action on the blood vessels of the hindlimb only through the nervous system. Small doses of angiotensin (0.1μg to 0.5μg i.v.) caused a nerve-mediated vasodilatation. A dose of 1μg of angiotensin caused immediate vasoconstriction in the perfused hindlimb. Small doses of noradrenaline (0.5μg to 1.0μg) caused slight vasodilatation; increasing the dose caused only a slight increase in vasodilatation. In all instances, the hindlimb effect was apparent within 5 minutes of the drug being given to the remainder of the animal; i.e., before the drug could reach the hindlimb in the perfusing blood. Both natural and synthetic angiotensin produced similar immediate vasoconstriction. Section of the nerves connecting the hindlimb to the remainder of the animal totally abolished the effects of angiotensin and noradrenaline, showing that these effects were mediated solely through the nervous system.

University of Otago
Dunedin, New Zealand

1011 Heimberg, Murray & Fizette, Norman B. **The action of norepinephrine on the transport of fatty acids and triglycerides by the isolated perfused rat liver.** Biochemical Pharmacology, 12:392–394, 1963.

To determine whether the transport and metabolism of lipids by the liver was affected by cathecholamines, the action of norepinephrine on the uptake of fatty acids and the release of triglycerides by the isolated perfused rat liver was studied. Male rats, 250 to 400 g in weight, were used as liver donors. Livers were removed and placed in a perfusion ap-

paratus. A constant infusion of 0.1μg l-norepinephrine bitartrate per 1 ml 0.9% sodium chloride per minute was started after maximum flow rates were maintained. The norepinephrine had a marked vasoconstrictor effect on the liver, which was alleviated by addition of 500μg phenoxybenzamine. Norepinephrine inhibited both triglyceride release and the rate of fatty-acid uptake.

Vanderbilt University School of Medicine
Nashville, Tennessee

1012 Hornbrook, K. R. & Brody, T. M. **Phosphorylase activity in rat liver and skeletal muscle after catecholamines.** Biochemical Pharmacology, 12:1407-1415, 1963.

The time course of liver phosphorylase activation after catecholamine administration, and the relative abilities of several adrenergic blocking agents to block catecholamine-indirect phosphorylase activation in liver and skeletal muscle were studied in intact, anesthetized female white rats (180 to 200 g in weight). Subcutaneously injected epinephrine and norepinephrine (500μg/kg) increased the liver phosphorylase activity, the peak effect occurring 10 minutes after injection. The liver phosphorylase levels were somewhat reduced 30 minutes after injection. Isoproterenol administration (10 or 25 mg/kg) did not increase the level of rat liver phosphoryline. Blood glucose changes after catecholamine treatment did not mirror the changes or lower phosphorylase activity. Complete blockade of the liver phosphorylase response to epinephrine was observed with the α-adrenergic blocking agent ergotamine (1.25 mg/kg). Phenoxybenzamine (5 or 20 mg/kg) and two β-adrenergic blocking agents, dichloroisoproterenol (10 or 25 mg/kg), and nethalide (10 mg/kg) gave partial blockade. The activation by epinephrine of skeletal muscle phosphorylase appears to be affected only by β-adrenergic blocking agents.

University of Michigan
Ann Arbor, Michigan

1013 Payne, Robert B. **Nutmeg intoxication.** New England Journal of Medicine, 269(1):36-38, 1963.

Two cases of nutmeg poisoning are reported in college students, 19 and 20 years old, who took the powdered spice to produce a sense of exhilaration and intoxication. About 14 g of powdered nutmeg suspended in milk was ingested. Symptoms, which began 5 hours later, included flushing of the skin, tachycardia, dry mouth, and CNS excitation. There were no apparent hallucinations or delusions, but both patients were agitated and apprehensive. Blood pressures were 170/90 and 152/84. Pulses were 130 and 148 per minute, temperatures were normal, and respiration was rapid. A sense of unreality persisted for from 48 to 60 hours after ingestion. Four weeks after poisoning, all laboratory tests were normal. Myristicin has been presumed to be the chief toxic component in nutmeg, but other volatile components, such as eugenol, isoeugenol, geraniol, safrol, borneal, and linalool, may also contribute to toxic effects on the central nervous system.

University of North Carolina
Student Health Service
Chapel Hill, North Carolina

1014 Kemali, D., Gaitonde, M. K., & Coppen, A. J. **The transfer of ^{35}S-methionine sulphone across the blood-cerebrospinal fluid barrier.** Journal of Neurology, Neurosurgery and Psychiatry, 26(3):220-222, 1963.

The rate of transfer of methionine sulfone from blood to lumbar cerebrospinal fluid was measured in 13 patients. The control group consisted of three psychiatrically normal male patients. Five male schizophrenic patients and five patients (1 female) suffering from organic disease of the nervous system were also tested. No patients had received drugs within 1 month of the test. A stock solution of S^{35}-methionine sulfone was diluted in a carrier to give a final concentration of 6μC/10 mg methionine sulfone/ml. A 5-ml portion of this solution was injected into an antecubital vein, and blood samples were withdrawn at frequent intervals from the opposite limb through an indwelling Gordh needle. Cerebrospinal fluid (10 ml) was withdrawn by lumbar puncture at either 1, 2, or 4 hours after the injection of the methionine sulfone. Results indicated that S^{35}-methionine sulfone entered the cerebrospinal fluid relatively slowly at a rate comparable to that found for sodium ions.

Medical Research Council
Surrey, England

1015 Harper, A. Murray & Bell, Ruth A. **The failure of intravenous urea to alter the blood flow through the cerebral cortex.** Journal of Neurology, Neurosurgery and Psychiatry, 26(1):69-70, 1963.

The brain cortex of each of five unselected mongrel dogs was exposed through a trephine hole made over the parietal lobe, and a piece of dura 1 cm in diameter was excised and replaced by a thin cellophane membrane. Cannulae were placed in the sagittal sinus, the superior thyroid branch of the carotid artery, and the femoral artery. The latter cannula was connected to a mercury manometer. The blood flow through the cortex was measured by the method of Lassen and Ingvar. After each blood-flow estimation, blood samples were taken from the aorta and sagittal sinus for measurement of carbon dioxide tension and oxygen content. After control measurements were made, 1.5 g/kg of lyophilized urea in 10% invert sugar was administered over a 10-minute period. Further measurements of blood flow and oxygen uptake were made at intervals of 5, 30, and 60 minutes. Within 5 to 10 minutes after the administration of urea, a dramatic shrinkage of the brain was observed. This reduction persisted for about 1 hour. There was a transient rise in blood pressure immediately after urea was given. No obvious change in either the blood flow or the oxygen uptake was noted after the administration of urea.

Glasgow Royal Infirmary
Glasgow, Scotland

1016 Spehlmann, Rainer. **Acetylcholine and prostigmine electrophoresis at visual cortex neurons.** Journal of Neurophysiology, 26(1):127-139, 1963.

Extracellular recordings were obtained from 113 neurons of the visual cortex of 52 cats (isolated brain) through one barrel of multibarreled micropipets while acetylcholine, prostigmine, and dihydro-β-erythroidine were expelled from adjacent barrels with weak anodic currents. In 20% of the neurons, spontaneous and evoked firing increased markedly during application of acetylcholine with currents that had no effect when led through a NaCl control barrel. Neuronal discharges evoked by illumination of the eye were facilitated by application of acetylcholine during the light-activated phase in type B (on) neurons, during the dark-activated phase in type D (off) neurons, and during both activated phases in type E (on-off) neurons. The short-latency response to stimulation by epicortical electrical shocks given with subthreshold intensity was also facilitated with acetylcholine. Facilitation of both light and epicortical-shock responses, as compared with NaCl controls, occurred with weaker acetylcholine iontophoresis than was required for activation of spontaneous firing in the same neuron. Prostigmine expelled from another barrel of the composite electrode often enhanced the effect of subsequently applied acetylcholine. Application of prostigmine without extrinsic addition of acetylcholine, however, sometimes had an activating and facilitating effect similar to that of acetylcholine. Acetylcholine and prostigmine or acetylcholine and dihydro-β-erythroidine were applied from several slightly varying electrode positions at the same neuron. Acetylcholine was effective only when it was applied in certain sites.

University of Freiburg im Breisgau
Freiburg im Breisgau, Germany

1017 Salmoiraghi, G. C. & Steiner, F. A. **Acetylcholine sensitivity of cat's medullary neurons.** Journal of Neurophysiology, 26(4):582-597, 1963.

Electrophoretic administration of chemical substances in the immediate vicinity of individual nerve cells in the cat's medulla revealed the presence of acetylcholine (ACh)-sensitive neurons. ACh-sensitive nerve cells were found scattered throughout the medulla, relatively more frequently in its cranial half, and intermingled with nerve cells that did not respond to electrophoretic administration of ACh. In five experiments in which the position of the electrode tip, when recording from an ACh-sensitive nerve cell, was determined histologically, it was found, in all five, that the tip of the electrode was in the reticular formation. Of 819 medullary nerve cells investigated, 584 (71.4%) did not show any appreciable change in their rate or pattern of discharge during ACh tests, whereas 180 (21.9%) increased and 55 (6.7%) decreased their rate of activity during ACh administration. Electrophoretic administration of physostigmine enhanced the response of ACh-sensitive nerve cells to ACh by increasing their firing rate while shortening the latency and prolonging the duration of their response to this substance, but had no enhancing effect upon the response of these units to methacholine. Electrophoretic administration of dihydro-β-erythroidine or hexamethonium to ACh-sensitive nerve cells blocked or reduced the ACh response of two-thirds of these neurons. Such blocking effects were reversible. Atropine had no significant effect on the response of ACh-sensitive units to ACh. Gallamine triethiodide disrupted the normal pattern of discharge of most cells tested so that evaluation of its effects on ACh responses was prevented. When thirty-four respiratory nerve cells were investiga-

ted, all but two (expiratory neurons) failed to show any obvious change in their patterns of activity during ACh tests.

National Institute of Mental Health
Washington, D.C.

1018 Liberson, W. T., Karczmar, A. G., Schwartz, E., & Ellen, P. **Synaptic transmission on the hippocampus and psychopharmacological agents.** International Journal of Neuropharmacology, 2(6):291-302, 1963.

The action of certain psychotropic agents on the amplitude and pattern of the potential evoked in response to transhippocampal stimulation, and on its facilitation and occlusion by a conditioning stimulus was studied. LSD-25 (0.5 to 10 mg/kg) did not affect the general pattern of facilitation and occlusion, nor was the amplitude of the evoked potential consistently effected. Similarly, chlorpromazine (2 to 8 mg/kg) had no consistent effect on the amplitude of the test stimulus response and no direct effect upon hippocampal synaptic potential. Marked increases as well as decreases of evoked potentials were noticed; moreover, changes in the polarity and in the complexity of the evoked potentials occurred in medicated animals more often than in control experiments.

Veterans Administration Hospital
Hines, Illinois

1019 Borsy, J., Huszti, Zs., & Fekete, M. **Antimescaline properties of some lysergic acid derivatives.** International Journal of Neuropharmacology, 2(6):273-277, 1963.

The antagonism of mescaline action by LSD, 2-bromo-LSD (BOL-148), 1-methyl-d-lysergic acid butanolamide, and dihydroergotamine (DHE) was studied in 160 mice on the scratch-reflex stereotype and on hypermotility during the orientation reflex. Central antiserotonin effect was measured according to Tedeschi et al.; peripheral antiserotonin effect was estimated from the decrease in serotonin-induced rat-paw edema. Results for the scratch-reflex stereotype showed that LSD was the most active antagonist of mescaline with an ED_{50} of 31µg/kg. BOL-148 was slightly less potent (ED_{50}, 80µg/kg), followed by DHE (ED_{50}, 84µg/kg, and the butanolamide derivative (ED_{50}, >500µg/kg). At 25µg/kg to 50µg/kg, LSD completely abolished mescaline hypermotility. A similar inhibition was elicited by BOL-148, but the dose required was 200µg/kg. Both LSD and BOL-148 inhibited the tremor elicited by the combined injection of iproniazid and 5HTP. The butanolamide derivative considerably reduced the edema elicited by serotonin and, at the same time, had no appreciable antimescaline effect.

Research Institute for Pharmaceutical Industry
Budapest, Hungary

1020 van Alphen, G. W. H. M., Robinette, Sarah L., & Macri, Frank J. **The adrenergic receptors of the intraocular muscles of the cat.** International Journal of Neuropharmacology, 2(6):259-272, 1963.

The nature of the adrenergic receptors of the internal muscles of the cat eye was investigated on isolated sphincter, dilator, and ciliary muscle strips by studying the effects of three sympathomimetic amines (l-epinephrine, l-norepinephrine, and l-isoproterenol) and the effects of three adrenergic blocking agents (phenoxybenzamine, tolazoline, and dichloroisoproterenol). One eye was enucleated from each of 134 young adult cats under anesthesia; the second eye was left in situ. After experiments were completed on the first eye, the animal was sacrificed, and the second eye was used. In addition, 13 cats were sympathectomized by excision of the superior cervical ganglion on one side. One eye was removed, either contralateral or ipsilateral, and the second eye was used as a control to evaluate the effects of denervation. Dilator-, sphincter-, and ciliary-muscle strips were made from all the eyes. The weights of the drugs given below are per milliliter of bath solution (oxygenated Krebs—Ringer solution maintained at 32° C). The three amines were applied to the strips in doses of 0.01µg to 10µg. The three adrenergic blocking agents were applied in doses of 10µg tolazoline, 1µg or 10µg phenoxybenzamine, and 1µg or 10µg dichloroisoproterenol. The six test compounds showed that all three muscles carry both alpha and beta receptors, the dilator being almost exclusively alpha and the sphincter and ciliary being predominantly beta in character. Supersensitivity of the pupil after ganglionectomy, present in vivo, was occasionally demonstrated in all three muscles in vitro.

National Institutes of Health
Bethesda, Maryland

1021 Schnieden, H. **The effect of alpha methyl dopa on experimental tremor.** Journal of Neurology, Neurosurgery and Psychiatry, 26(6):500-504, 1963.

The effect of α-methyldopa on the tremor produced in mice by several pharmacological agents is noted. Tremor was induced in male mice (20 to 40 g) by the i.p. injection of the following drugs: tremorine dihydrochloride, 40 mg/kg: nicotine hydrogen tartrate, 15 mg/kg; harmine, 30 mg/kg; 5HTP, 200 mg/kg; and methylamphetamine, 20 mg/kg. Two doses of l-α-methyldopa, 200 and 35 mg/kg, were given i.p.; 1.5 mg/kg atropine, used for comparison, was given s.c. Tremor was measured by a modification of the method of Ahmed and Taylor; the sedative effect of α-methyldopa was tested by the method of Dews. Mice were observed at various intervals after α-methyldopa; all animals were allowed food and water freely up to 1 hour before measurement of tremor. The results showed that the tremor induced by methylamphetamine, tremorine, or nicotine was not modified by pretreatment with α-methyldopa (200 mg/kg). The latter drug did, however, modify the tremor produced by harmine and 5HTP. The main effect of α-methyldopa appears to be on the 5HTP tremor-producing pathway; it is ineffective against the muscarinic and nicotinic pathways. When α-methyldopa was given at a dose level of 200 mg/kg, it had a sedative effect; this effect was markedly less when the drug was given at a dose level of 35 mg/kg.

Institute of Neurology
Queen Square, London, England

1022 Wada, Juhn A., Hill, Donald, & Wrinch, John. **Reversal by atropine of 5-hydroxytryptophan-induced behavioral changes in cats and monkeys.** Journal of Neuropsychiatry, 4(6):413-415, 1963.

The purpose of this report is to show that atropine, which reduces cholinergic activity, would almost completely eliminate the behavioral effects of 5HTP. Three domestic cats and 2 monkeys (Macacque and African green) were trained for 12 months in performing a conditioned avoidance response and an approach behavior, respectively. After termination of a control run, all animals were injected i.p. with 10 to 15 mg/kg 5HTP plus 50 mg/kg vitamin B_6. Performance rate was studied 30 minutes after injection and hourly thereafter until predrug levels were reached. In cats, a slight depression of performance followed a dose of 10 mg/kg 5HTP, and a profound deterioration occurred with 15 mg/kg. Peak deterioration occurred 2 to 3 hours after injection and returned to normal within 5 to 8 hours. In monkeys, similar deterioration was observed, with a peak 2 to 2-$\frac{1}{2}$ hours after drug. In cats, injection of 0.05 to 0.75 mg/kg of atropine alone produced a minor reduction in performance, and in monkeys, 0.1 to 0.3 mg/kg of this agent alone had no effect. Simultaneous injection of atropine and 5HTP, however, reduced or completely eliminated the effects of 5HTP. It is postulated that the central effect of serotonin is secondary to the functional alteration of the cholinergic system.

The University of British Columbia
Vancouver, Canada

1023 Steiner, William G. & Himwich, Harold E. **Effects of antidepressant drugs on limbic structures of rabbit.** Journal of Nervous and Mental Disease, 137(3):277-284, 1963.

Six compounds (imipramine, amitryptyline, opipramol, desmethylimipramine, desmethylamitriptyline, and chlorprothixene) which, because of a substitution in one or both bridges between benzene rings of the phenothiazine nucleus, have additional antidepressant action, were tested in 84 New Zealand male albino rabbits weighing 3 kg. An additional 100 rabbits received 20 other compounds that were mostly modifications of phenothiazine for background evaluation. The animals were artificially respired, and each of the 26 drugs was administered to groups of five rabbits each by the femoral vein at a rate of 1.0 mg/kg every 4 minutes until the animals succumbed. EEG recordings were taken continuously. All compounds were found to be indistinguishable from each other in EEG blocking and arousal. Many also evoked varying kinds of dysrhythmic EEG patterns. A small number of EEG seizures were recorded for drugs of the phenothiazine structure, but imipramine-like drugs with antidepressant action evoked seizures in nearly 100% of the animals. These latter compounds also evoked spike-like EEG patterns in olfactory bulbs. All these drugs have a basic tranquilizing action. In conclusion, many drug actions are shared by this heterogenous group of compounds, irrespective of their specific clinical use.

Galesburg State Research Hospital
Galesburg, Illinois

1024 Shuster, Frederick, Napier, Edward A., Jr., & Henley, Keith S. **Serum transaminase activity following morphine, meperidine and codeine in normals.** American Journal of Medical Sciences, 246(6):714-716, 1963.

This paper determines the effect of three analgesics (codeine, meperidine, and morphine) commonly used in controlling pain of myocardial infarction on serum glutamic-oxalacetic transaminase (SGOT) and serum glutamic-pyruvic transaminase (SGPT) levels. All three drugs were tested on all subjects to detect differences in response. Six healthy male students without previous history of hepatobiliary disease were given codeine sulfate (64 mg), meperidine HCL (100 mg), or morphine sulfate (10 mg) s.c. at intervals of at least 48 hours. Blood samples were drawn 0, 2, 4, 6, and 24 hours after injection, and SGOT and SGPT activities were then determined. There was no significant rise in either SGOT or SGPT activity after injection of any of the three analgesics. In addition, there were no significant differences in response among the three drugs in any given subject. Administration of these drugs should not interfere with determinations of transaminase activity in patients with suspected myocardial infarction, unless they have concomitant biliary-tract disease or have undergone a previous cholecystectomy.

University of Michigan Medical School
Ann Arbor, Michigan

1025 Vincent, William A., Kashemsant, Udomporn, Cuddy, Richard P., Smulyan, Harold, & Eich, Robert H. **The acute hemodynamic effects of l-alpha methyldopa.** American Journal of Medical Sciences, 246(5):558-568, 1963.

This study investigates the acute hemodynamic effects of l-α-methyldopa in 11 labile hypertensive patients, 9 men and 2 women (26 to 66 years old), in both the supine and semierect positions. All had a blood presure of 150/90 or higher on admission, and none had been an antihypertensive therapy for at least 2 weeks. Six patients were given 500 mg of l-α-methyldopa hydrochloride ester and five patients were given 750 mg, all by slow i.v. injection. Six hours later (maximum blood-pressure effect), with patients resting 20 minutes in the supine position, cardiac output and direct arterial pressure were measured. Five minutes later, nine patients were tilted head-up 90° and arterial pressures were monitored for 8 minutes; then pressure was recorded and a second cardiac-output determination was made. Mean blood pressure was reduced in both positions after the drug: reduction was greater in the tilted position, with systolic pressure decreasing more than diastolic. Lowering the supine blood pressure occurred with cardiac-output reduction but without a decrease in total peripheral resistance in seven of the eight patients who responded. The greater reduction in mean blood pressure with tilting occurs without a greater reduction in cardiac output because of lowered peripheral resistance. From its CNS, cardiac, and peripheral arteriolar effects, l-α-methyldopa has a complex mode of action and several sites of action.

State of New York Upstate Medical Center
Syracuse, New York

1026 Duke, Martin, Ames, Richard P., & Abelmann, Walter H. **Hemodynamic effects of methoxamine in normal subjects.** American Journal of Medical Science, 246(3): 301-307, 1963.

The hemodynamic effects of methoxamine (pressor response and bradycardia) were studied in normal subjects. Eight normal subjects received 9.0 to 20.7 mg of methoxamine i.v. over a period of 30 to 54 minutes. The mean arterial pressure rose 19%, the mean venous pressure rose 48%, the heart rate fell 22%, the cardiac index was unchanged, and the "central" blood volume rose 11%. Derived values indicated a significant rise in stroke index, in total systemic resistance, and in left ventricular stroke work. The effects of the drug appeared to be dose-dependent. In the presence of bradycardia, the maintenance of cardiac output need not be due to a positive inotropic action, but may be related to the lengthened diastolic filling period, increased filling pressure, and elevated "central" blood volume. Although the uniform increase in venous pressure may indicate ventricular failure in the face of increased systemic vascular resistance without a positive inotropic effect, seven of eight normal subjects increased stroke volume and thus maintained cardiac output. The results obtained here differ from those of a similar study by Stanfield and Yu, and possible reasons for the differences are given.

Massachusetts Memorial Hospitals
Boston, Massachusetts

1027 Sprince, Herbert, Parker, Clarence M., Jameson, Dorothy, & Alexander, Fred. **Urinary indoles in schizophrenic and psychoneurotic patients after administration of tranylcypromine (Parnate) and methionine or tryptophan.** Journal of Nervous and Mental Disease, 137(3):246-251, 1963.

Urinary-indole-excretion patterns were examined in four chronic schizophrenics and two psychoneurotics (controls) to correlate in-

dole excretion with behavioral change. Disturbed indole metabolism has long been implicated in schizophrenia. Weekly urine specimens (collected for 24 hours on the seventh day) were obtained in a double-blind, six-by-six, Latin-square design. During a series of six weekly test periods, with a rest week between the third and fourth test weeks, patients received daily oral doses of either placebo, tranylcypromine (10 mg t.i.d.), l-tryptophan (5 gm t.i.d.), l-methionine (6.6 gm t.i.d.), tranylcypromine plus l-tryptophan, or tranylcypromine plus l-methionine. A 24-hour control urine sample was taken the week preceding the test. A combination of tranylcypromine plus l-methionine gave definitely higher urinary levels of tryptamine and indoleacetic acid than either component alone. This effect occurred in all subjects except one schizophrenic, and was related to onset of mental symptoms in both groups. This result is interesting because of a previous finding that urinary tryptamine and indoleactic acid levels become elevated in exacerbation of psychotic symptoms. The psychotic N,N-dimethyl derivatives of tryptamine or serotonin were not found. There was a marked increase in indoleacetamide after tryptophan in the two psychoneurotics but not in the four schizophrenics. (More information is needed in the reliability of the Latin-square method for future studies.)

Veterans Administration Hospital
Coatesville, Pennsylvania

1028 Lang, W., Gershon, S., & Holan, G. **Some antagonists of atropine-like psychotomimetics.** Journal of Pharmacy and Pharmacology, 15:831-840, 1963.

Because of the interest in the atropine-like psychotomimetics and their antagonists, the actions of atropine and an antiacetylcholine drug, ethylpiperidylcyclopentyphenyl glycolate hydrochloride (JB-329), were contrasted and compared, and the pharmacology of their antagonists was investigated. Conscious dogs were used to observe behavioral and pharmacological effects. Blood pressures from anesthetized dogs and cats were recorded. Studies were also made in human volunteers, in which blood pressure and ECG's were recorded continuously. Isolated strips of fundus from the rat stomach were used to record the effect of drugs on contractions from 5HT. All drugs were administered i.v. in varying doses. The actions of the antagonists 1,2,3,4-tetrahydro-5-aminoacridine, p-phenylmandelic acid, 2- and 3-phenanthrylglycolic acids, and phenoxymandelic acid were compared. The peripheral pharmacological effects of JB-329 were essentially similar to those of atropine. In the same dose, both drugs slightly raised blood pressure, reduced pulse pressure, induced marked tachycardia, and produced the other autonomic changes expected of atropine and atropine-like compounds. Both drugs also inhibited parasympathetic effects and acetylcholine responses and produced potentiation of the pressor responses to adrenaline and noradrenaline. In addition to direct cholinergic effects, the antagonists were found to inhibit the adrenergic responses potentiated by JB-329 and atropine.

University of Melbourne
Melbourne, Australia

1029 Gunne, L. M. & Jonsson, J. **Effects of reserpine in rats pretreated with α-methyldopa.** (Letter) Journal of Pharmacy and Pharmacology, 15:774-775, 1963.

A further demonstration of a central action of the α-methylated catecholamines is given in which rats were pretreated with α-methyldopa before a depletion of the catecholamine stores was produced by reserpine. The rats (300 g in weight) were given 150 mg/kg α-methyldopa i.p. at 9:00 A.M. on the first 2 days, followed by 300 mg/kg at 4 P.M. on the second day. On the third day, these rats and untreated controls were given 2 mg/kg reserpine i.p. Before reserpine, all rats appeared normal. After reserpine, controls were deeply sedated, with decrease in muscular tone, eyelid ptosis, and diarrhea. Pretreated rats developed exophthalmos, a catatonic-like state (increase in muscle tone), and an absence of diarrhea. After 24 hours, however, all rats were mildly sedated and had diarrhea---both groups were indistinguishable. The syndrome in pretreated rats has been tentatively ascribed to liberation of α-methylated catecholamines in the brain. Since α-methyldopamine disappears 16 to 20 hours after α-methyldopa, the signs were probably caused by α-methylnoradrenaline, which is not attacked by MAO.

Karolinska Institute
Stockholm, Sweden

1030 Ferrini, R. & Glässer, A. **Action of guanethidine on the 5-hydroxytryptamine content of the brain.** (Letter) Journal of Pharmacy and Pharmacology, 15:772-773, 1963.

The effect of guanethidine on the 5HT content of the rat brain was compared with the effect of α-methyldopa and reserpine. Three

groups of white rats, grouped by weight, were treated as follows: (1) male rats (200 to 300 g) were given saline (controls, N=24), guanethidine (10 mg/kg for 7 days, N=16), α-methyldopa (200 mg/kg for 7 days, N=8), and reserpine (1 mg/kg for 7 days, N=8); (2) female rats (280 to 320 g) were given saline (controls, N=6) and guanethidine (10 mg/kg for 12 days, N=6); and (3) male rats (140 to 160 g) were given saline (controls, N=8) and guanethidine (10 mg/kg for 7 days, N=8). Guanethidine decreased cerebral 5HT content in rats in both sexes weighing more than 200 g, but had no effect on rats weighing 140 to 160 g. Reserpine and α-methyldopa were more effective in reducing 5HT. Why guanethidine is effective in the heavier rats is inexplicable. Perhaps guanethidine reacts with only part of the amines present if one considers that there are two pools of amines, exogenous and endogenous, in the neoplastic mast cells.

Farmitalia Research Laboratories
Milan, Italy

1031 Agarwal, Sohan L., Deshmankar, B. S., & Bhargava, Vinod. **Chloroquine in bronchial asthma.** (Letter) Journal of Pharmacy and Pharmacology, 15:693, 1963.

Chloroquine, an antiasthmatic drug that posesses antihistaminic and antianaphylactic activities, was injected in male albino rats to see if histamine, which produces allergic reactions, was reduced in quantity by chronic administration of the drug. Chloroquine sulfate (5 mg/kg) was injected i.p. into eight rats for 21 days, and saline was injected into eight control rats. (All rats weighed 100 to 125 g.) The animals were killed on the 21st day, and samples of lung and stomach were pooled, extracted, and assayed for histamine. Chloroquine caused a significant reduction in histamine content of the lung, but an increase in histamine content of the stomach. These results substantiate its value in bronchial asthma.

G. R. Medical College
Gwalior, India

1032 Medaković, M. & Banić, B. **The effects of two phenylacetic acid derivatives on the analgesic action of morphine in mice.** Journal of Pharmacy and Pharmacology, 15:660-665, 1963.

Two phenylacetic acid esters, diethylaminoethylphenyldiallyl acetate (CFT 1201) and diethylaminoethylphenylallyl acetate (CFT 1208), injected i.p. (50 mg/kg) in male white mice potentiated the analgesic action of 0.5μg of morphine injected into the posterior portion of the brain 90 minutes later. When the phenyl acetates (50μg) were injected into the brain, they potentiated the analgesic action of morphine injected s.c. (10 mg/kg) 80 minutes later. When morphine was injected intracerebrally, the effect was dose-dependent. All measurements of analgesic effect were based on the method of Woolfe and Macdonald (53° C hotplate).

Medical Faculty
Belgrade, Yugoslavia

1033 Farmer, J. B. & Petch, B. **Interaction of cocaine and tyramine on the isolated mammalian heart.** Journal of Pharmacy and Pharmacology, 15:639-643, 1963.

Guinea pig hearts were perfused with Krebs' solution by the method of Langendorff. Tyramine hydrochloride (in 100μg doses) was injected into a cannula close to the heart every 5 to 10 minutes. In some experiments, cocaine hydrochloride was added to the reservoir of Krebs' solution in the required concentration. The noradrenaline content of the whole heart was estimated fluorimetrically by the method of Merrills. Perfusion of cocaine (1μg/ml to 10μg/ml) through isolated guinea pig hearts antagonized the action of tyramine in reducing the noradrenaline content of the heart. The extent of antagonism was proportional to the dose of both compounds. Cocaine exerted its antagonistic action at concentrations that had no effect on the release of noradrenaline from the isolated heart. These results may account for the antagonism of the sympathomimeter actions of tyramine by cocaine.

Charles F. Pfizer, Ltd.
Kent, England

1034 Day, M. D. & Rand, M. J. **Awakening from reserpine sedation by α-methyldopa.** (Letter) Journal of Pharmacy and Pharmacology, 15:631-632, 1963.

The hypothesis that a metabolite of α-methyldopa, α-methylnoradrenaline, is able to occupy storage sites in peripheral tissues normally occupied by noradrenaline and is then available for release from these stores by stimuli that normally release noradrenaline was investigated. Reserpine-treated rats were injected with α-methyldopa, and the responses to sympathetic nerve stimulation

and to indirectly acting sympathomimetic amines were observed. In heavily sedated rats (55 g in weight) treated with 15 mg/kg reserpine i.p., α-methyldopa (250 mg/kg i.p.) caused a gradual increase in motor activity. Injections of α-methyldopa in rats not treated with reserpine decreased motor activity. It was concluded that metabolites of α-methyldopa may serve as "false transmitters" in the CNS as well as at peripheral adrenergic nerve endings.

School of Pharmacy
Brunswick Square
London, England

1035 Vogin, Eugene E. & Smooklen, Harold. **Sympathomimetic activity of guanethidine.** (Letter) Journal of Pharmacy and Pharmacology, 15:561-562, 1963.

To study the proposed sympathomimetic activity of guanethidine, the effect of the drug on cardiac activity was measured in mongrel dogs of both sexes pretreated with reserpine. Arterial blood pressure and flow and chronotropic and inotropic activity were measured on each dog. Guanethidine sulfate (15 mg/kg) produced a biphasic blood-pressure response. There was an initial depressor response lasting 1 to 3 minutes, followed by a pressor response lasting as long as 45 minutes. Accompanying the depressor response were marked increases in both chronotropic and inotropic activity of the myocardium and a vasodilation. These effects decreased as the blood pressure reverted toward a pressor response. To assess the possibility of β-receptor activity, pronethanol (5 mg/kg), a specific β-receptor blocking agent, was injected i.v. before guanethidine was given. There was no change in the depressor response, but the pressor response was markedly reduced. The chronotropic response was blocked and a negative inotropic response prevailed. Guanethidine, in addition to catecholamine-depleting activity, does possess some direct sympathomimetic action.

University of Pittsburgh
Pittsburgh, Pennsylvania

1036 Dagirmanjian, R. **The effects of guanethidine on the noradrenaline content of the hypothalamus in the cat and rat.** Journal of Pharmacy and Pharmacology, 15:518-521, 1963.

Because there are conflicting reports about whether guanethidine causes a depletion of noradrenaline in the brain, further experiments are given on the effect of acute and chronic administration of guanethidine in cats and rats on the content of noradrenaline in the hypothalamus. Single doses of 15 mg/kg guanethidine i.p. were given to male or female cats weighing 1.7 to 2.8 kg. Single doses of 5 and 15 mg/kg i.p. were given to female albino rats weighing 175 to 225 g. Both groups of animals were also given guanethidine chronically, 15 mg/kg s.c. daily for 7 days. Controls were given 0.9% saline solution. At various times up to 72 hours after a single injection in the cats, the noradrenaline content was not lowered in the hypothalamus, but was significantly lowered in the superior cervical ganglia. After 7 days of daily injections, however, there was a significant decrease in hypothalamic noradrenaline. Attempts to lower the hypothalamic noradrenaline in rats after single or daily injections were unsuccessful. Overt signs in cats indicated depression of the sympathetic nervous system. Both cats and rats had diarrhea.

The University of Rochester
Rochester, New York

1037 Mantegazza, P. & Riva, M. **Amphetamine-like activity of β-phenethylamine after a monoamine oxidase inhibitor.** Journal of Pharmacy and Pharmacology, 15:472-478, 1963.

In an investigation of the amphetamine-like effects of β-phenethylamine, anorexigenic activity was studied in male Wistar rats and in adult mongrel dogs of both sexes. In addition, female rats and Swiss mice of both sexes were used in the study of locomotor activity and hyperthermia. Iproniazid was injected s.c. 24 hours before the injection of β-phenethylamine hydrochloride; dosage was 200 mg/kg (rats and mice) or 129 mg/kg (dogs). Amphetamine and β-phenethylamine were administered s.c. over a range of doses; isotonic saline was used in controls. To measure hyperthermia, rats or mice were fasted for 12 hours prior to a 5-hour monitoring of rectal temperature. The drugs were injected after the basal temperature had been taken twice. Spontaneous activity was measured in mice by a method similar to that described by Dews. A technique similar to that of Di Ferrante and Longo was used to measure anorexigenic activity in dogs. After pretreatment with iproniazid, β-phenethylamine induced an increase of coordinated spontaneous motility in mice, anorexia in rats and dogs, and hyperthermia in mice and rats. Also, β-phenethylamine exhibited a difference in lethality between isolated and aggregated mice. These effects were seen with similar

doses of β-phenethylamine or amphetamine. Unlike amphetamine, β-phenethylamine does not increase spontaneous activity in rats.

University of Milan
Milan, Italy

1038 Leme, J. Garcia & Rocha e Silva, M. **Effect upon the analgesic action of reserpine of central nervous system stimulants and drugs affecting the metabolism of catechol- and indole-amines.** Journal of Pharmacy and Pharmacology, 15:454–460, 1963.

In this study of reserpine action, male white mice (15 to 20 g in weight) were tested by a hot-plate method; reaction time (RT) was measured from the time the animal was placed on the plate until it presented a sign of discomfort. Drug solutions were prepared so that each animal received a maximum of 1 ml i.p. Reserpine was given in a single dose of 5 mg/kg, and RT was measured 24, 48, and 72 hours postinjection. Animals treated with MAO inhibitors and reserpine received two divided doses of the inhibitor 24 and 2 hours before the reserpine. Animals previously injected with reserpine received CNS stimulants in three doses, each given 30 minutes before tests for RT. Mice treated with reserpine and LSD-25 were put into two groups: one received reserpine and a single dose of LSD-25 30 minutes before the first hot-plate exposure; the other received reserpine and then a dose of LSD-25 30 minutes before each of three RT tests. Animals treated with 5HTP or DOPA received one dose a day for 3 days before the reserpine. A control group of 100 animals was exposed to the hot plate three times at intervals of 24 hours. The MAO inhibitors, iproniazid, SKF 385, pheniprazine, and 2596 IS decreased RT values. The CNS stimulants also reduced the analgesic effect 24 and 48 hours after reserpine but not after 72 hours. LSD-25 markedly inhibited reserpine action; no difference was observed when used as a single dose or with repeated daily doses. The analgesic effect of reserpine was greatly inhibited by 5HTP but DOPA had no action.

University of Sao Paulo Ribeirão Prêto
Sao Paulo, Brazil

1039 Chodera, A. **Blockade of 5-hydroxytryptamine antidiuresis in rats by 2-bromlysergic acid diethylamide tartrate and 1-methyl-lysergic acid butanolamide.** Journal of Pharmacy and Pharmacology, 15:386–389, 1963.

The effects of 2-bromlysergic acid diethylamide (BOL 148) and 1-methyllysergic acid butanolamide (UML 491) on 5HT antidiuresis were studied in 72 male white rats (150 and 250 g in weight). The rats were fasted for 12 hours before the experiments. Immediately after fasting, they were given a water load of 5 ml distilled water per 100 g body weight through a stomach tube. Rats were kept three to a cage. The urine drained directly into a measuring cylinder, and the volume was recorded every 15 minutes for 4 hours. Rats that excreted less than 50% of the water load in the first 100 minutes were excluded. The drugs were given immediately after the water load: 5HT as the creatinine sulfate, 1 mg/kg s.c.; BOL 148, 5 mg/kg i.p.; UML 491, 2.5 mg/kg i.p.; and posterior pituitary extract, 1 unit/kg s.c. Control groups received isotonic saline. Room temperature was kept between 16° and 18° C. After a single injection of 5HT, BOL 148 and UML 491 counteracted the induced antidiuresis. The antidiuretic effect of posterior pituitary extract was not blocked or diminished by the lysergic acid derivatives. Used alone, BOL 148 and UML 491 had neither diuretic nor antidiuretic action.

Medical Academy
Poznan, Poland

1040 Onuaguluchi, G. & Lewis, J. J. **Some aspects of the pharmacology of orphenadrine.** Journal of Pharmacy and Pharmacology, 15:329–336, 1963.

The effects of orphenadrine on skeletal muscle, with some observations upon its anticonvulsant action and its effects upon spinal reflexes, are considered. The effects of orphenadrine on: (1) suxamethonium-induced contracture and neuromuscular block, (2) tubocurarine-induced neuromuscular block, and (3) response to indirect tetanization were studied in the hen and cat gastrocnemius muscle-sciatic nerve preparations. Orphenadrine was also studied in a frog rectus abdominis muscle preparation, an isolated rat phrenic nerve-diaphragm preparation, on the patellar and crossed extensor reflexes in the cat, and on leptazol seizures and electroshock convulsions in mice. Orphenadrine possesses muscle-relaxant activity resembling that of tubocurarine in preparations of the hen, rat, and frog. It antagonizes suxamethonium-induced contracture in the hen, but increases the duration of depression of the twitch height. The bearing of these findings upon antiparkinsonian activity and other uses of orphenadrine are discussed.

University of Glasgow
Glasgow, Scotland

1041 Day, M. D. & Rand, M. J. **A hypothesis for the mode of action of α-methyldopa in relieving hypertension.** Journal of Pharmacy and Pharmacology, 15:221-224, 1963.

Responses to tryamine are not greatly affected by the α-methyldopa depletion of noradrenaline. After injection into conscious cats and rats, α-methyldopa does not cause any striking effects indicative of sympathetic-nerve blockage. When the contractions of the cat's nictitating membrane were studied, stimulation of the postganglionic nerves produced an impairment of responses that was evident at low frequencies of nerve stimulation. There was, however, little or no impairment of responses to high frequencies of stimulation that produced maximal responses. Indirect evidence was obtained that α-methyldopa can be converted to α-methylnoradrenaline, and that the α-methylnoradrenaline formed can be used as a transmitter at sympathetic-nerve endings. When the pressure activity of α-methylnoradrenaline was compared with that of noradrenaline, it was found to have about half the potency in cats, about one-third in rats, and about one-sixth in guinea pigs and rabbits. Because of the lesser potency of α-methylnoradrenaline, there is some loss of responsiveness to sympathetic-nerve stimulation.

University of London
London, England

1042 Ayton, John P. & Marshall, P. B. **Analeptic activity of tremor-producing amino-alcohols.** (Letter) Journal of Pharmacy and Pharmacology, 15:217-218, 1963.

The amino-alcohols 1,1,3-triphenyl-3-aminopropan-1-ol (PROP) and 1,1,2-triphenyl-2-aminoethanol (ETH) were tested for analeptic activity against pentobarbitone anesthesia by the mouse-awakening test of Goodwin and Marshall. The median lethal doses of ETH and PROP, when injected i.v. into mice, were, respectively, 24.5 and 17.5 mg/kg. This compares with 4.5 mg/kg for picrotoxin. The analeptic potency of ETH and PROP was of the opposite order to their tremor-producing potencies, ETH having about 80% and PROP about 50% of the activity of picrotoxin.

Queen's College
Dundee, Scotland

1043 Bhagat, B. **Influence of guanethidine on the catecholamine depleting effects of tyramine in the rat heart.** (Letter) Journal of Pharmacy and Pharmacology, 15:152, 1963.

Male Holtzman rats (200 to 225 g in weight) were given guanethidine sulfate (5 mg/kg, i.v.) 20 minutes before the i.m. injection of tyramine hydrochloride (20 mg/kg). Thirty minutes after tyramine administration, the animals were killed by decapitation. The concentrations of catecholamines in the ventricular myocardium were determined by the trihydroxyindole fluorimetric procedure of Shore and Olin. The results showed that guanethidine had no influence on the depleting effects of tyramine in the rat heart.

University of Wisconsin
Madison, Wisconsin

See also: 803, 829, 850, 886, 919, 971, 1044, 1047, 1048, 1051, 1056, 1058, 1059, 1063, 1065

1044 Kato, R., Chiesara, E., & Vassanelli, P. Mechanism of potentiation of barbiturates and meprobamate actions by imipramine. Biochemical Pharmacology, 12:357-364, 1963.

The potentiating action of imipramine on the pentobarbital effect was studied in female, Sprague--Dawley rats. Carisoprodol and meprobamate were suspended with 1% carboxymethylcellulose solution, and other drugs were dissolved in distilled water. Drugs were injected i.p. The determinations of hexobarbital, pentobarbital, carisoprodol, and meprobamate were carried out according to the methods of Axelrod et al., Brodie et al., Kato et al., and Hoffman and Ludwig, respectively. Liner enzyme activities were determined by measuring the metabolized drugs in liver slices or in the microsomal preparation after an incubation of 1 hour. Drug effects were determined by duration of loss of the righting reflex. Imipramine markedly potentiates the action of hexobarbital, pentobarbital, meprobamate, and carisoprodol, but it does not potentiate the action of barbital and chloralhydrate. Unlike SKF 525-A, imipramine can reinduce sleep in rats awakening from pentobarbital hypnosis. Imipramine inhibits the microsomal drug-metabolizing enzymes as well as the in vivo metabolism of pentobarbital and meprobamate. It potentiates the inhibitory actions of SKF 525-A and phenylisopropylhydrazine on the metabolism of hexobarbital and meprobamate. In the imipramine treated rats, carisoprodol, hexobarbital, meprobamate, and pentobarbital concentrations in the brain, determined on recovery from the loss of the righting reflex, are a little lower than in controls.

University of Milan
Milan, Italy

1045 Michaelson, I. Arthur & Whittaker, V. P. **The subcellular localization of 5-hydroxytryptamine in guinea pig brain.** Biochemical Pharmacology, 12:203-211, 1963.

The subcellular distribution of 5HT in subfractions from guinea pig-brain homogenates was assayed by fluorometric techniques. Results were in close agreement with earlier studies employing the rat-fundus-strip-bioassay method. Results of the present study showed that the distribution of 5HT in the particulate and soluble fractions was 74% and 26%, respectively. The particulate fractions were free of myelin and mitochondria and were identifiable as consisting largely of pinched-off nerve endings. Iproniazid raised the level of 5HT in brain tissue, but did not alter the subcellular distribution.

Agricultural Research Council
Institute of Animal Physiology
Babraham, Cambridge, England

1046 De Fanti, David R. & De Feo, John J. **Urinary dopamine levels and kidney monoamine oxidase activity in hypertensive rats.** Biochemical Pharmacology, 12:173-177, 1963.

The relationship among urinary dopamine levels, arterial blood pressure, and kidney MAO activity was studied in male albino Sprague--Dawley rats with experimentally induced renal hypertension. Dopamine was extracted from urine and measured according to the method of Carlsson and Waldeck. The MAO levels in kidney were determined according to Cotzias and Dole. Urinary dopamine levels rose throughout the experimental period from an average control value of 673μg/l to a high of 1,022μg/l. The excretion of dopamine was found to be quite variable. As the weight of the experimental animals increased, the urinary dopamine levels (mg/kg/24 hours) increased, whereas in the sham-operated control animals, the urinary excretion of dopamine decreased with increasing weight. The kidney MAO activity decreased after the induction of hypertension, went through what appeared to be a compensatory rise, and then dropped off sharply to the end of the experimental period. A clear relationship was not established between decreased MAO activity and urinary dopamine levels.

University of Rhode Island
Kingston, Rhode Island

1047 Rosenblum, Ira & Stein, Arthur A. **Preferential distribution of diphenylhydantoin in primary human brain tumors.** Biochemical Pharmacology, 12:1453–1454, 1963.

Samples of primary brain tumors and adjacent areas of normal brain tissue were obtained from eight patients during surgery. Seven of the patients had ostrocytomas of grades III and IV and one had a meningioma. Analysis of diphenylhydantoin was made by the method of Dill et al. Average recovery of drug added to normal brain tissue in a concentration of 2.5μg/g was 86.2%, with a standard error of 3.1%. The concentrations of the drug were higher in tumor tissues than in normal brain tissues of all patients. In mice bearing tumors of nonneural origin (adenocarcinomas of the breast), the drug showed a greater predilection for brain tissue. In mice bearing Perese ependymomas, the mean tumor to brain drug ratio was 0.86±0.18.

Albany Medical College
Albany, New York

1048 Eiduson, Samuel, Geller, Edward, & Wallace, Raymond D. **The quantitive determination and excretion of some phenothiazine type drugs in neuropsychiatric patients.** Biochemical Pharmacology, 12:1437–1439, 1963.

The spectrophotometric method of Eiduson and Wallace was used to estimate the amount of unconjugated phenothiazine metabolites in the urine of neuropsychiatric patients. After the administration of a single-400 mg dose of thioridazine tablets, excretion of metabolites reached a peak within 24 hours. When the sustained release form of the drug was given, the peak of excretion was 36 hours postadministration. When the drug was administered in either form at a continuing dose of 200 mg b.i.d., marked fluctuations appeared, with the excretion peak reached after 1 week. For 70-day continuous dose data, a correlation of 0.73 was obtained between drug excretion and urine volume. When 26 different samples were obtained from a chlorpromazine patient (over a 1-month period), it was found that 37% of the total urinary excretion was apparently conjugated as the glucuronide (range, 15% to 49%). The percentage of the drug excreted as the glucuronide remained essentially the same over a wide range of drug. When S^{35}-ring-labeled thioridazine was administered, less than 3% of the metabolites in the urine were not extractable by chloroform.

University of California
Los Angeles, California

1049 Wurtman, Richard J. & Axelrod, Julius. **A sensitive and specific assay for the estimation of monoamine oxidase.** Biochemical Pharmacology, 12:1439–1441, 1963.

An assay for MAO, utilizing the measurement of deaminated C^{14}-metabolites of C^{14}-tryptamine, is described. Sixty or more assays, each requiring as little as 5μg of tissue, can be performed in 3 hours. Tissues are homogenized in chilled isotonic potassium chloride, and 1μl to 100μl are used for assay; C^{14}-tryptamine, 1.3 mC/mmole, is dissolved in water and stored at -4° C. In a typical assay, 25μl of enzyme preparation, 25μl of C^{14}-tryptamine, and 250μl of 0.5 M phosphate buffer (pH 7.4) are mixed in a glass-stoppered centrifuge tube and incubated at 37° C for 20 minutes. The reaction is stopped by an addition of 0.2 ml of 2 N hydrochloric acid. The deaminated radioactive material is extracted into 6 ml of toluene by shaking. After centrifugation, a 4-ml aliquot of the organic layer is transferred to a vial containing 10 ml of phosphor and counted for 1 to 5 minutes in a liquid-scintillation spectrophotometer. A small amount of C^{14}-tryptamine is extracted by this procedure. A correction is made for this blank value by incubating C^{14}-tryptamine with boiled enzyme. The reaction was linear with time for at least 20 minutes and with enzyme concentration over a range of 5μg to 1,000μg of liver. This assay can be used whether or not aldehyde dehydrogenase is present.

National Institute of Mental Health
Bethesda, Maryland

1050 Eiduson, Samuel & Geller, Edward. **The excretion and metabolism of ^{35}S-labeled thioridazine in urine, blood, bile, and feces.** Biochemical Pharmacology, 12:1429–1435, 1963.

A single oral dose of S^{35}-ring-labeled thioridazine was administered to neuropsychiatric patients; a patient having an indwelling catheter was the subject of the urine and feces experiments; a different patient with a bile-duct cannula was the subject for the bile-fluid studies; a third patient was used for the serum (and urine) studies. The first patient received 112μC in a total dose of 400 mg of drug; the other two patients each received 100μC in a 200-mg total dose. Results showed that 30% of the original thioridazine dose is excreted in the urine and 50% is excreted in the feces. About 60% of the drug passes through the bile fluid. Only about 3% of the original dose remains in the

serum at peak levels, which were reached 3 to 4 hours after administration. Radioautograms and chromatograms of a urinary extract indicate a congruity between radioactive metabolites and acid chromogens and that urinary metabolites differ qualitatively from those found in feces and bile. Chloroform extracts over 97% of the urinary activity. This agrees with the observation that little or no glucuronide-conjugated material appears in the urine after oral thioridazine.

University of California
Los Angeles, California

1051 Wurtman, Richard J. & Axelrod, Julius. **Sex steroids, cardiac ^{3}H-norepinephrine, and tissue monoamine oxidase levels in the rat.** Biochemical Pharmacology, 12:1417-1419, 1963.

Groups of six or seven male and female Sprague—Dawley rats (100 g) were surgically gonadectomized under pentobarbital anesthesia. In other similar groups, estradiol pellets (25 mg) were implanted s.c. in males and testosterone pellets (25 mg) were implanted in females. Sham-operated animals served as controls. After 5 weeks, all rats gained 110 to 160 g except the males treated with estradiol, which gained only 60 g. Animals were killed by neck fracture, the presence of the pellet material was verified, and their livers were homogenized in chilled isotonic potassium chloride and assayed for MAO. To study the relation between cardiac MAO activity and H^3-catecholamine levels, mature rats (200 g in weight) were given 0, 1, or 10 mg/kg of β-phenylisoprophlhydrazine i.m. 18 hours before receiving 10μC/100 g of dl-H^3-norepinephrine hydrochloride. Rats were sacrificed 48 hours later and MAO was determined on aliquots of cardiac ventricle. Hepatic MAO activity is greater in male than in female rats; this difference can be reversed by chronic administration of an opposite sex steroid. When the MAO activity of rat heart is 90% inhibited, the rate of disappearance of H^3-catecholamine from this tissue is reduced; 50% inhibition has no effect on this rate. Since sex differences in MAO activity are less than 50%, these differences are probably of little physiologic significance.

National Institute of Mental Health
Bethesda, Maryland

1052 Rupp, W. Dean & Handschumacher, R. E. **Two different metabolic fates of 5-ethyl-6-azauracil in mice.** Biochemical Pharmacology, 12:13-18, 1963.

Metabolites from 5-ethyl-6-azauracil (EtAzU) were obtained after the i.p. injection of 1 ml of a neutral aqueous solution of EtAzU (20 mg/ml) into each of five Swiss Webster male mice (20 to 35 g in weight). The mice were kept in plastic cages for 24 hours, and urine was collected on sheets of filter paper. During the collection period, the animals were allowed water but not food. The urine was eluted by homogenizing the filter paper with water in a blender and by evaporating the eluate under reduced pressure to a final volume of 10 ml. The recovery of EtAzU and its metabolites was judged to be about 70% to 90%. Two metabolites and the unchanged drug were detected in the urine. The major metabolite, 5-(1-hydroxyethyl)-6-azauracil, accounted for about 70% of the recovered material, and the minor metabolite, 5-ethyl-6-azauracil-1-ribofuranoside, accounted for 1% to 3%.

Yale University School of Medicine
New Haven, Connecticut

1053 Carlini, E. A. & Green, Jack Peter. **Acetylcholine activity in the sciatic nerve.** Biochemical Pharmacology, 12:1367-1376, 1963.

Measurements of the acetylcholine (Ach) activity in fractions obtained from centrifuged homogenates of the rabbit sciatic nerve, and measurements of the distribution of Ach activity along segments of these nerves are presented. Rabbit sciatic nerves were homogenized in sucrose solution containing 0.35μg/ml or 1.4μg/ml physostigmine and were centrifuged into three fractions——sediment, particulate fraction, and supernatant solution. Either acetone or 5% trichloroacetic acid was used to extract Ach, and paper chromatographs were made of the extracts. Bioassay for Ach activity was performed on guinea pig ileum and frog rectus abdominis muscle. The Ach activity was uniformly distributed along the course of the nerves, whether high or low concentrations of physostigmine were used in the homogenate; the bioassay also revealed uniform distribution of Ach along the sciatic nerve. Measured on the ileum, 75% of the Ach activity was found in the soluble portion of the cell; on the rectus abdominis, the corresponding figure was 35%. Total Ach equivalents are higher when measured on rectus abdominis than on ileum. It is suggested that sciatic nerve contains a substance other than Ach to which the frog rectus abdominis muscle is sensitive.

Yale University School of Medicine
New Haven, Connecticut

1054 Utley, John D. **Gamma aminobutyric acid and 5-hydroxytryptamine concentrations in neurons and glial cells in the medial geniculate body of the cat.** Biochemical Pharmacology, 12:1228–1230, 1963.

GABA and 5HT concentrations were measured in neurons and glial cells of the medial geniculate body of the cat. The AI, AII, Ep, SII, temporal, and insular cortical areas were removed from cat brains, which resulted in degeneration and gliosis of the principal division of the medial geniculate body. The degenerative process leaves only glia, presynaptic axon tips from inferior colliculus neurons and a few neurons. Slightly more than 500μg of GABA occurs in 1 g of medial geniculate tissue and is concentrated only about 10% by allowing intact neurons to degenerate. GABA is apparently distributed equally between neurons and glia. About 1.20μg of 5HT occurs in 1 g of medial geniculate tissue, and removal of neurons concentrates it by 72%. When neurons and axon tips are removed by inducing lesions of the brachium of the inferior calliculus, 5HT is still concentrated in the medial geniculate. Most of the 5HT is apparently contained in the glial cells.

Duke University Medical Center
Durham, North Carolina

1055 Elison, Christian & Elliott, Henry W. **N- and O-demethylation of some narcotic analgesics by brain slices from male and female Long-Evans rats.** Biochemical Pharmacology, 12:1363–1366, 1963.

N-demethylation of morphine, codeine, and meperidine and O-demethylation of codeine were studied in brain slices from male and female Long—Evans rats to determine, in part, the mechanism of action of narcotic analgesics. Brain tissue was taken from normal male and female rats and from male rats made tolerant to 100 mg/kg morphine/day. Tissue was incubated aerobically in the following substrates: morphine-N-$C^{14}H_3$, codeine-N-$C^{14}H_3$, codeine-N-$C^{14}H_3$, and meperidine-N-$C^{14}H_3$. Average amounts of morphine demethylated by normal and tolerant rats were not appreciably different; brain-enzyme activity was unimpaired by tolerance. There was no parallelism between potency of the narcotic and the extent to which it was demethylated by the brain; both meperidine and codeine were demethylated to a greater extent than the more potent morphine, and male rats were capable of greater demethylation of morphine than female rats. O-demethylation of codeine occurred to a lesser extent than N-demethylation. It is suggested that the demethylating enzymes of brain and liver may be identical.

San Francisco Medical Center
San Francisco, California

1056 D'Iorio, A. & Mavrides, C. **Actions of the thyroid hormones and analogues in vitro on catechol-O-methyltransferase.** Biochemical Pharmacology, 12:1307–1313, 1963.

The actions of 3,5-diiodothyronine, 3,3',5-triiodothyronine, and thyroxine and their formic, acetic, and propionic acid derivatives on catechol-O-methyltransferase (COMT) were studied in vitro. Purified rat liver COMT was prepared and assayed by the methods of Axelrod and Tomchick. Epinephrine (0.5×10^{-4} M to 3×10^{-4} M) and S-adenosylmethionine (S-AME) (1×10^{-4} M to 1×10^{-3} M) were used as substrates. The formic, acetic, and propionic acid derivatives, 3,5-diiodothyronine, and 3,3',5-triiodothyronine inhibited COMT; thyroxine alone was ineffective. The type of inhibition and the inhibition constant (K_i) are listed for each compound; K_i is also given for the two substrates.

University of Ottawa School of Medicine
Ottawa, Canada

1057 Barchas, Jack D. & Freedman, Daniel X. **Brain amines: Response to physiological stress.** Biochemical Pharmacology, 12:1232–1235, 1963.

Several different physiological stressors were studied for their effect on levels of serotonin and norepinephrine in the brains of 200 g male Sprague—Dawley rats. The following stressors were used: swimming to exhaustion in 15° and 23° C water; running to exhaustion on a 12-inch diameter treadmill; immersion in chest-high water at 15° C; exposure of shaved animals to a 4° C environment for 3 to 5 hours; food and water deprivation for 72 hours; and anoxia induced in a nitrogen chamber. Norepinephrine and serotonin were assayed in the same brain by fluorescence spectrometry according to the method of Mead and Finger. Changes found by this nethod were confirmed by other standard methods (Bogdanski et al. and Crout et al.). In rats swum to exhaustion, serotonin level increased about 15% and norepinephrine level decreased 20%. The pattern of change is similar to that induced by the psychotomimetic drugs. Treadmill rats showed 10%

changes in both amines. Rats in 15° C, chest-high water showed amine-level changes like those in rats swum to exhaustion at 15° C. The other stressors produced no significant changes. Changes in brain-amine level correlated with changes in behavioral state.

Yale University School of Medicine
New Haven, Connecticut

1058 Mirkin, B. L. & Gillis, C. N. **The subcellular localization of tritium after incubation of homogenates of rat brain with ^{3}H-norepinephrine.** Biochemical Pharmacology, 12:1173–1179, 1963.

To investigate the possibility that exogenous norepinephrine may be bound to subcellular structures, rat-brain homogenates incubated with tritium-labeled norepinephrine, at 37° or 4° C were subjected to density-gradient centrifugation, and the distribution of tritium in specific subcellular fractions determined. Five distinct fractions were produced, designated by the letters A, B, C, D, and E; the subfractionation method is described. After incubation at 37° C, the homogenates revealed an uneven distribution of tritium among the five fractions. The bulk (76%) of the tritium was in fractions A and B; B contained 46% of the total tritium in the gradient. Pretreatment of the rats with reserpine, or incubation of the homogenate at 4° C, decreased the percentage of tritium in fraction B to 36%. The percentage distribution of tritium was not influenced by a fiftyfold increase in H^{3}-norepinephrine added to incubation medium. Since over 80% of the tritium in fractions A and B could be accounted for by unchanged norepinephrine, it is suggested that the distribution of tritium in brain homogenates may accurately reflect that of endogenous catecholamine in intact neural structures.

Yale University School of Medicine
New Haven, Connecticut

1059 McMahon, R. E. **The demethylation in vitro of N-methyl barbiturates and related compounds by mammalian liver microsomes.** Biochemical Pharmacology, 12:1225–1228, 1963.

The role of oxidative enzyme systems present in microsomal fractions from rat and rabbit livers in the demethylation in vitro of N-methyl barbiturates and related compounds was studied. N,N'-dimethylbarbital was chosen as the model substrate. This compound, in the presence of NADPH, oxygen, and liver microsomes, was demethylated, but at a rate much lower than that for a typical amine, such as butynamine. The maximum rate of demethylation was 21 mμmoles/minute/g liver for N,N'-demethylation, 4.5 mμmoles/minute/g liver for N-methylbarbital, and 316 mμmoles/minute/g liver for butynamine. The effects of various inhibitors on the demethylation of dimethylbarbital are tabulated; the inhibition is similar to that observed in other microsomal oxidations. Seven other amides and related compounds were examined as possible substrates for rabbit- and rat-liver microsomal N-demethylase, and results are tabulated. Demethylation was concluded to be catalyzed by liver microsomes; the mechanism proposed involves direct hydroxylation of the methyl group as the initial reaction step.

Eli Lilly and Company
Indianapolis, Indiana

1060 Ryall, R. W. **The identification of acetylcholine in presynaptic terminals isolated from brain.** Biochemical Pharmacology, 12:1055–1056, 1963.

Studies were run in an attempt to prove that the cholinomimetic activity of presynaptic terminals is chiefly due to acetylcholine (ACh). The cholinomimetic substance was extracted from the crude mitochondrial fraction of the rat brain by heating the fraction at 100° C for 10 minutes at pH 4; on subfractionation, the cholinomimetic activity is recovered from a layer of the density gradient that corresponds to presynaptic terminals. Parallel assays of the extract were run on superfused guinea pig ileum, the blood pressure of rats treated with neostigmine, superfused frog rectus abdominis muscle in which the cholinesterase was inactivated by tetraethylpyrophosphate, and on eserinized rabbit auricles; the ACh content was 0.9μg/g brain. The effects produced by the extract were similar to those produced by ACh with regard to rate of onset, duration of action, blocking by atropine, potentiation by eserine, and destruction by alkali. Since parallel biological assays distinguished among all choline esters examined, including pyruvylcholine and those reported to be present in brain extracts, it was concluded that the cholinomimetic activity of an extract of presynaptic terminals was due to ACh and not to a related ester.

Australian National University
Canberra, Australia

1061 Musacchio, J. M. & Goldstein, M. **Biosynthesis of norepinephrine and norsynephrine in the perfused rabbit heart.** Biochemical Pharmacology, 12:1061-1063, 1963.

To determine whether organs innervated by sympathetic nerves are able to perform all the enzymatic steps from tyrosine to norepinephrine, rabbit hearts were perfused with C^{14}-dopamine, C^{14}-tyramine, and C^{14}-tyrosine, and the formation of catechols and β-hydroxylated compounds was investigated. From 1% to 3% of the administered C^{14}-dopamine was converted to norepinephrine, which accumulated in heart tissue; no norepinephrine was found in the perfusate. After perfusion with C^{14}-tyramine, norsynephrine was isolated in heart tissues; neither C^{14}-dopamine nor C^{14}-norepinephrine was detected in heart tissue or the perfusate. After perfusion with C^{14}-tyrosine, the compounds, C^{14}-norepinephrine, C^{14}-dopamine, and C^{14}-DOPA, were isolated from heart tissue, and C^{14}-DOPA was isolated from the perfusate. This study shows that the heart was capable of performing all the enzymatic reactions necessary for the biosynthesis of norepinephrine: tyrosine → DOPA → dopamine → norepinephrine.

New York University College of Medicine
New York, New York

1062 Burkman, A. M. **Loss of biological activity of apomorphine from auto-oxidation.** Journal of Pharmacy and Pharmacology, 15:461-465, 1963.

The activity of apomorphine metabolites as pecking-syndrome stimulants in birds is known; this study was undertaken to determine whether the products of the spontaneous oxidation of apomorphine retain the ability to initiate the avian syndrome. Buffered and unbuffered solutions of apomorphine hydrochloride in psysiological saline were incubated at 30° C for 61 days, and samples were periodically withdrawn for both chemical and biological assay. Unoxidized apomorphine was estimated spectrophotometrically according to a modification of Kaul et al. Groups of adult domestic pigeons of mixed sex were used in the biological assay. The loss of biological activity, as measured by the gradual diminution in the intensity of the pecking syndrome in pigeons, paralleled the disappearance of unoxidized apomorphine. The unbuffered solutions retained about 75% of their biological activity after 61 days incubation, but solutions buffered initially to pH 6.0 were biologically inert after 16 days. Extracted and concentrated degradation products, when administered to pigeons, failed to initiate the pecking syndrome.

University of Illinois
Chicago 12, Illinois

1063 McMahon, Robert E., Marshall, Frederick J., Culp, Hilman W., & Miller, Warren M. **The metabolism of nortriptyline-N-methyl-^{14}C in rats.** Biochemical Pharmacology, 12:1207-1217, 1963.

Nortriptyline--N-methyl-C^{14} was synthesized, and its metabolism, distribution, and excretion were studied in Wistar strain rats. In vitro studies were run on rat-liver microsomes to determine N-demethylase activity. Respired radiocarbon dioxide, tissue-residue, and urinary-, biliary-, and fecal-excretion studies were performed in vivo, and urinary metabolites were identified. About 25% of a dose of nortriptyline undergoes N-demethylation in the whole animal. Another 40% is excreted in urine as conjugates of the cis and trans isomers of 10-hydroxynortriptyline. Distribution studies revealed that the drug undergoes wide distribution, with highest concentrations in lung and liver. The drug was identified in the brain, showing that it passes the blood-brain barrier. It was also found to be slowly, but efficiently, absorbed from the intestinal tract.

The Lilly Research Laboratories
Indianapolis, Indiana

1064 Beani, Lorenzo & Bianchi, Clementina. **The extraction of acetylcholine in small samples of cerebral tissue.** (Letter) Journal of Pharmacy and Pharmacology, 15:281-282, 1963.

Guinea pigs of either sex (270 to 330 g in weight) are decapitated and the skull is opened with scissors. Cerebral tissue, 50 to 100 mg, is excised, weighed, and immersed for 2 to 3 minutes in 3 ml of McIlvaine's citric acid-didodium phosphate buffer. After homogenization and cooling, the container is washed with 3 ml of Tyrode solution without glucose and bicarbonate, but with a double concentration of salts, to obtain an isotonic medium. The supernatant is diluted with normal Tyrode solution and assayed on guinea-pig ileum against either the standards or freshly prepared solutions of acetylcholine. The assay is done at intervals of 90 to 120

seconds. The contractions are recorded with an isotonic level, 1:20 magnification (loaded at 0.40 to 0.50 g) writing on a smoked drum. The average recovery of the standards, against known solutions of acetylcholine, was 101.3%±17% (S.D.), so it is clear that this extraction method releases only small amounts of interfering substances and does not cause loss. When extracts were assayed on the brain tissue and the terminal ileum, the average recovery of the standard was 90%±22% (S.D.).

University of Florence
Florence, Italy

1065 Hupka, S. & Dumont, J. E. **In vitro effect of adrenaline and other amines on glucose metabolism in sheep thyroid, heart, liver, kidney and testicular slices.** Biochemical Pharmacology, 12:1023–1035, 1963.

Stimulation of glucose catabolism in thyroid slices by adrenaline, noradrenaline, and serotonin; the effects of adrenaline on the catabolism of glucose by sheep thyroid, heart, kidney cortex, liver, and testicular slices; and the physiological meaning of these effects were investigated in vitro. Adrenaline, noradrenaline, and serotonin stimulate the oxidation of glucose carbon 1 and glucose carbon 6 by thyroid tissue of various species. The effect of adrenaline depends on its prior oxidation to adrenochrome. A similar but weaker glucose carbon 1 oxidation by liver and kidney cortex slices was observed. Stimulation of glucose carbon 1 oxidation by MAO substrates was seen in thyroid and testis slices. The glycogenolytic effect of adrenaline on liver and heart tissue was demonstrated by an increased glucose output by liver slices and a decreased glucose uptake by heart slices in the presence of this hormone. The biological significance of adrenaline on glucose catabolism is discussed, and it was concluded that only the glycogenolytic effect is physiological.

Brussels University School of Medicine
Brussels, Belgium

1066 Seeman, Philip M. & Bialy, Harvey S. **The surface activity of tranquilizers.** Biochemical Pharmacology, 12:1181–1191, 1963.

It was observed that all tranquilizers lower the surface tension of a Ringer solution in close correlation with their clinical antipsychotic potency, regardless of whether they are phenothiazines or not. These surface-tension observations are reported, along with some observations on the surface tension of schizophrenic plasma. Primary attention has been on these antipsychotic neuroleptic compounds: reserpine, chlorpromazine, butyrylperazine, ethopropazine, fluphenazine, propiomazine, prochlorperazine, thioridazine, trifluperazine, triflupromazine, and carphenazine. For comparison, the mild tranquilizers, such as chlordiazepoxide and promazine, have been included. Surface tension was measured by the Wilhelmy plate method. The potent neuroleptic drugs tried all lowered the surface tension of a Ringer solution, pH 7, at concentrations between 10^{-7} and 5×10^{-6} M. Nonneuroleptics (imipramine, trimeprazine, promazine, chlordiazepoxide, promethazine, and toluidine blue) lowered the surface tension concentrations ranging from 2×10^{-5} to 5×10^{-4} M. Chlorpromazine sulfoxide barely lowered surface tension at 10^{-3} M. The surface tension of schizophrenic plasma was normal and did not change when phenothiazine was added. Urine tension fell upon addition of phenothiazine.

The Rockefeller Institute
New York, New York

See also: 803, 850, 886, 984, 994, 999, 1000, 1001, 1006, 1007, 1008, 1009, 1010, 1011, 1012, 1016, 1023

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PSYCHOPHARMACOLOGY ABSTRACTS

Vol. 3 No. 6

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REVIEWS, SUMMARIES, BIBLIOGRAPHIES, GENERAL ARTICLES AND BOOKS

1067 Moya, F. & Thorndike, V. **The effects of drugs used in labor on the fetus and newborn.** Clinical Pharmacology and Therapeutics, 4(5):628-653, 1963.

This review is limited primarily to drugs of interest to the obstetrician and anesthesiologist in the management of pain relief during labor and delivery. Factors in the reaction of infants to drugs are discussed under the following headings: drugs and their antagonists; transfer across the placenta; distribution, absorption, and excretion; drug metabolism; stimulation of enzyme activity; and birth asphyxia. Relaxants of skeletal muscle discussed are curare, gallamine triethiodide, decamethionium iodide, and succinylcholine chloride. Gaseous and volatile anesthetics discussed are nitrous oxide and ethylene, cyclopropane, ether, chloroform, trichloroethylene, and halothane. Included in the barbiturates are the long-, intermediate-, short-, and ultrashort-acting types. In the tranquilizer category are chlorpromazine, promethazine, propiomazine, perphenazine, prochlorperazine, promazine, hydroxyzine and meprobamate, and reserpine. Chloral hydrate, ethyl alcohol, paraldehyde, dimenhydrinate, and thalidomide are among the hypnotics and sedatives given. Narcotics and their antagonists are also discussed. Miscellaneous drugs, such as belladonna alkaloids, local anesthetics, and respirating gases, are included in the review. (236 references)

The Presbyterian Hospital and Sloane Hospital for Women
New York, New York

1068 Wagner, Henry N., Jr. **Radioactive pharmaceuticals.** Clinical Pharmacology and Therapeutics, 4(3):351-370, 1963.

General principles regarding the use of radiopharmaceuticals are discussed, with emphasis being given to the role of radioisotopes in diagnostic procedures. Among the topics covered are radiation safety, radiation detection, pharmaceutical properties, renal disease, cardiovascular disease, measurement of cardiac output, measurement of regional blood flow, thyroid disease, hematologic disease, gastrointestinal disease, malabsorption of fat, excessive intestinal secretion, and neurological disease. (58 references)

The Johns Hopkins University School of Medicine
Baltimore, Maryland

1069 West, G. B. **Studies on the mechanism of anaphylaxis: A possible basis for a pharmacologic approach to allergy.** Clinical Therapeutics, 4(6):749-783, 1963.

This review deals with the basic mechanisms of allergic reactions through anaphylaxis, with the hope of developing a more effective pharmacological approach to their prevention and treatment. Topics discussed include the antigen-antibody combination, types of anaphylaxis biochemical mechanisms of anaphylaxis, anaphylaxis and histamine, anaphylaxis and mast cells, anaphylaxis and 5HT, slow-reacting substances, anaphylaxis and accessory agents, the anaphylactoid reaction, anaphylaxis and hormones, and the physiological significance of histamine and 5HT. Conclusions concerning each topic are given. (287 references)

University of London
London, England

1070 Laurence, D. R. & Webster, R. A. **Pathologic physiology, pharmacology, and therapeutics of tetanus.** Clinical Pharmacology and Therapeutics, 4(1):36-72, 1963.

Experimental evidence for the transport of tetanus toxin from its formation site to the CNS is reviewed. An attempt is made to correlate the mode of action of the toxin with that of drugs used to suppress convulsions. An attempt is also made to evaluate the principal controversial therapeutic techniques. Topics discussed are site of action of tetanus toxin, transport of tetanus toxin (in local and general tetanus), mode of action of the toxin, causes of death, pharmacology of tetanus convulsions, treatment of tetanus,

antitoxins, care of wounds, chemotherapy, choice of anticonvulsant, neuromuscular blocking agents, tracheostomy, and andrenocortical steroids. Whether death is inevitable in some cases of tetanus or whether toxic effects are reversible if the patient is kept alive long enough remains unknown. (412 references)

University College Hospital Medical School
London, England

1071 Friend, Dale G. **Drugs and the fetus.** Clinical Pharmacology and Therapeutics, 4(1):141-148, 1963.

This review considers some of the drugs that may affect the fetus by passing through the placental barrier. The following types of pharmacologic agents are discussed: drugs acting on the CNS, drugs acting on the cardiovascular system of the fetus, sympathomimetic amines, anticoagulants, sulfonamides and antibiotics, thyroid drugs, and miscellaneous drugs acting on the fetus. The effects of nicotine and some heavy metals are mentioned briefly.

Peter Bent Brigham Hospital
Boston, Massachusetts

1072 Prankerd, T. A. J. **Hemolytic effects of drugs and chemical agents.** Clinical Pharmacology and Therapeutics, 4(3):334-350, 1963.

Three different modes of action by which red cells are destroyed in the body by chemical agents are discussed, and, where possible, chemical agents known to produce hemolytic reactions are included. In many instances, however, it is impossible to assign a particular mechanism to a particular agent. Sections are presented on background history, pathogenesis, recognition of anemia, agents having a direct effect against red cells of all individuals, hemolytic anemia due to interaction between the chemical agent and defective red cells and due to formation of antibody, and drugs causing hemolytic anemia through unknown mechanisms. It is concluded that the rapid growth of knowledge in this field in the past 10 years has revealed chemical bases for individual susceptibility to several groups of drugs and has had wide repercussions in other scientific fields. (138 references)

University College Hospital Medical School
London, England

1073 Lewis, J. J. **Centrally acting drugs.** Science Progress, 51(204):551-565, 1963.

Although they may also possess transmitter activity, compounds and interrelationships discussed here are almost certainly involved in cellular metabolism. Topics discussed include the function and levels of GABA in the brain, the metabolism of nervous tissue and neuronal activity, the oxidation of glucose and the synthesis of adenosine triphosphate, effects of centrally acting drugs on phosphate metabolism, and other biochemical considerations. A table presents examples of contemporary drugs used for the treatment of mental illness, which are grouped by class and by specific use. The article concludes with the statement that nothing is known for certain about the precise mechanism of action of drugs that act on the CNS because of the limitations of present knowledge of the physiology and biochemistry of the CNS. Until the basic mechanisms are worked out, the deliberate and specific design of chemicals for their pharmacological and therapeutic properties in the brain cannot be made.

University of Glasgow
Glasgow, Scotland

1074 Bain, W. A. & Doughty, R. B. **The testing of tranquillizers.** Practitioner, 190:29-35, 1963.

In the testing of tranquilizers, it is stated that there are many problems: measurements of effects on psychoses and psychoneuroses are still imprecise; animal tests are not always thorough enough for interpolation to humans; and, since these drugs are prescribed for long use, laboratory and clinical testing must be prolonged. Discussions are given of the ways of seeking new tranquilizers, initial testing, multiple test procedures, toxicity tests, and human trials (initial human pharmacology, determination of therapeutic use, and expansion of clinical use). The testing design outlined represents at least 3 to 5 years work. Several thousand animals will have been used in the preclinical and clinical phases, and one to two thousand patients will have received treatment with the new agent. If the drug is approved for marketing, it is still not completely assessed---this can be done only after widespread clinical use for several years. Ironically, the rate of progress is such

that before that time has elapsed, however useful the drug is, something even better is probably on the way.

Smith Kline & French Research Institute
Welwyn Garden City, Pennsylvania

1075 Hollister, Leo E. & Prusmack, John J. **Psychotherapeutic drugs in the treatment of depressions.** Clinical Medicine, 70(10):1805-1817, 1963.

When the patient is mildly depressed, a course of dextroamphetamine in dosages of 5 to 15 mg, never exceeding 30 mg, daily is preferred. Similar doses of pipradrol are needed. When the patient is moderately or severely depressed, either imipramine, amitryptiline, the hydrazides, or possibly tranylcypromine should be used. The hydrazides suggested are nialamide (50 mg t.i.d. up to a total daily dose of 600 mg), isocarboxazid (5 mg t.i.d. up to 50 mg), and phenelzine (10 mg t.i.d. up to 75 mg). The amphetamine or piperidine stimulants may cause nervousness and irritability in some patients. Tolerance may develop on prolonged use, leading to an increased dosage and to addiction. Schizophrenia-like psychoses may develop with an increased dosage of amphetamines, and convulsions have followed their abrupt withdrawal. The hydrazides may overstimulate, produce manic reactions, and cause such side reactions as postural hypotension, blurring of vision, urinary hesitancy, and constipation. Imipramine produces an intrahepatic obstructive jaundice and agranulocytosis. Side reactions include hypotension, delayed urination, and blurred vision.

Veterans Administration Hospital
Palo Alto, California

1076 Smith, Jackson A., Foster, Merritt W., Jr., & Rudy, Lester H. **Tranquilizers and energizers---or neither?** Postgraduate Medicine, 16(4):347-354, 1963.

This review included three discussions by three psychiatrists. The first is an introduction commenting on the increasing use of tranquilizers today---they are considered the drugs in "fashion." Tranquilizers are valuable adjuncts to psychotherapy, but if overused, they can obscure and encourage the fixation of a sick pattern of thinking and feeling. The second discussion gives the writer's experience with the tranquilizers reserpine, prochlorperazine, trifluoperazine, promazine, meprobamate, chlorpromazine, chlorprothixene, and chlordiazepoxide. The third discussion encompasses energizers and antidepressants, depressive states (physiologic or normal depression, neurotic depression, and psychotic depression), and major classifications of drugs used in depressive states (CNS stimulants, MAO inhibitors, and iminodibenzyl derivatives). It is stated that the antidepressants affect target symptoms of depression but not the underlying process.

Illinois State Psychiatric Institute
Chicago, Illinois

1077 Blair, Donald. **Drugs for depression.** (Letter: comment on letter by William Sargant.) British Medical Journal, 1(5335):945, 1963.

The following observations have been made in this correspondence, concerning drugs prescribed for depression: (1) There is an optimum dose for each patient. (2) Maintenance dosage must be continued in endogenous depression until such time as the depression would have cleared up, under ordinary circumstances, spontaneously. (3) Patients must always be gradually weaned from the drug. (4) It is not advisable to use MAO inhibitors in combination with imipramine or amitriptyline. (5) When dexamphetamine or other amphetamines are prescribed, the patient should be advised that the drug will be withdrawn after a few weeks. (6) A phenothiazine should be given with imipramine or amitriptyline to counteract the agitation often concomitant with depression. (7) Imipramine, when used in conjunction with electroconvulsive therapy, is effective in curing chronic depression.

St. Bernard's Hospital
Southall, Middlesex, England

1078 Rogg, Sanford G. & Pell, Sidney. **Use of psychotropic drugs by employed persons.** Industrial Medicine and Surgery, 32:255-260, 1963.

In a survey of 3,042 white-collar employees of the du Pont Company, about 25% used one or more psychotropic drugs within a year. Increased drug usage with increasing age was noted, it being higher among women than men at all ages. About 60% of the drug users listed frank emotional conditions as the reason for taking the drug. The most frequently cited conditions were nervousness, insomnia, unexplained tension, gastrointestinal disorders, and hypertension. About

50% had taken the drugs for less than 1 month. Eighty percent of the users of the drugs believed them beneficial; there was a slightly higher percentage among those taking barbiturates and psychic energizers than those taking tranquilizers. Among the drug users, there was an increased consumption of alcohol with age and a greater use of alcohol by persons with a "free-floating" type of anxiety than by those having psychosomatic conditions. A survey of 3,104 male production workers of a large factory revealed that 16% used psychotropic durgs.

E. I. du Pont de Nemours and Company, Inc.
Wilmington, Delaware

1079 Boericke, Garth M. **Tranquilizing drugs used homeopathically and homeopathic tranquilizers.** Hahnemannian, 98: 5-8, 1963.

The use of homeopathic principles with ataractic drugs may open a new modern field for the practicing physician. In the case of a retired physician of 84, hospitalized with senile symptoms following several genitourinary operations, heavy sedation and the homeopathic drugs, such as lachesis, sulfur, and hyoscyamus, failed to help. Chlorpromazine in usual doses aggravated his condition. A 5X homeopathic dilution of chlorpromazine poured over discs was given every 3 hours, and within 24 hours, his mind cleared to a large extent, and his dehydrated physical state cleared up. In certain cases, chlorpromazine produces persistent and fantastic dreams, the paradoxical effects of constipation and diarrhea, polyphasia, and anorexia, and it may act as an antiemetic, or may produce vomiting. Ten percent of cases showed dermatitis, especially aggravated in summer. One patient with edema and swelling of hands on contact with any cold object received very favorable results with homeopathic administration of histamine phosphate. Aside from nasal stuffiness, dizziness, and drowsiness, reserpine may cause mental difficulty and depression, suicidal tendencies, and melancholy. Homeopathic tranquilizers are: sepia, pulsatilla, nux vomica, lycopodium, and zinc.

1011 Arch Street
Philadelphia 7, Pennsylvania

1080 Watson, John. **The role of bemegride in the treatment of barbiturate overdosage.** (Letter) Medical Journal of Australia, 1:950-951, 1962.

Observations of more than 150 patients in coma induced by overdosage of a variety of agents showed that, in profound coma, the patient becomes hypothermic as well as hypotensive, and that parallel fluctuations occur in temperature, blood pressure, and pulse rate. Massive overdoses of sedative depress all metabolic and cellular activities of the body, resulting in a sharp fall in heat production. Heat loss is facilitated by concomitant peripheral vasodilatation, perhaps due to autonomic block. It may be postulated that the vasodilatation results in hypotension. It is irrational to interfere therapeutically, as with the use of neurostimulants and weak convulsive agents (e.g., bemegride), with a single manifestation (hypotension) of a state affecting every cell in the body to some degree, a state in which the operative mechanisms appear to be homeostatic and mutually protective.

Queen Elizabeth Hospital
Woodville, South Australia

1081 O'Malley, Pearse. **Problems in the management of psychiatric patients in a general hospital. (A fifteen year survey---1946-1961).** Journal of the Irish Medical Association, 52:83-86, 1963.

A broad outline is given of the problems involved in the management of psychiatric patients in a general hospital. New drugs developed during the past 10 years have expanded the range of patients that could be hospitalized and managed, and have eliminated much of the need for electroconvulsive therapy. In 1948, i.v. barbiturates combined with paraldehyde were found most effective in managing acute psychiatric cases. Thiopental sodium and curare (12 mg) were given in electroconvulsive therapy. Since January 1953, succinylcholine (15 mg for women and 25 mg for men) has been given a short time after i.v. administration of 3 ml thiopental sodium in electroconvulsive therapy. Apnea lasting 10 to 15 minutes occasionally occurs with succinylcholine. More recently, Brietal, a short-acting barbiturate, has been used in place of thiopental sodium. Imipramine was discontinued in conjunction with electroconvulsive therapy because peripheral cyanosis developed, which did not respond to oxygenation. Violent outbursts following electroconvulsive therapy are managed with thiopental sodium.

Mater Hospital
Belfast, Ireland

1082 Pogge, Raymond C. **The toxic placebo. Part I---Side and toxic effects reported during the administration of placebo medicine.** Medical Times, 91:1-6, 1963.

Side effects and toxic effects that occurred during administration of placebos were tabulated from the statistics presented in 67 publications. In 3,549 people, 38 different side effects were attributed to placebo, 9 of them with an incidence of 1.0%. The most common side effects, listed in order of decreasing incidence, were drowsiness, headache, nervousness and insomnia, nausea, constipation, vertigo, dry mouth, gastrointestinal distress, and anorexia. The incidence of side and toxic effects from placebo should be kept in mind when the significance of isolated complaints of side effects that occur during administration of medication is being evaluated.

Dorsey Laboratories
Lincoln, Nebraska

1083 Pogge, Raymond C. **The toxic placebo. Part II---The case of the partial patient.** Medical Times, 91:6-9, 1963.

In a previous report on side and toxic effects from placebo, 18 reports could not be included because of technical problems of communications; i.e., numbers with respect to side effects could not be tabulated. This finding is the basis for the present article, in which the presentation of numerical data in these reports are discussed; they are: listing the partial patient (for example, 10% of 24 patients or 2.4 patients), unique methods of presenting statistics, absence of figures for individual side effects, complete absence of numerical values, incomplete reporting, tabulation in terms of total doses given rather than number of patients studied, and ambiguous sample size.

200 North 15th Street
Lincoln, Nebraska

1084 Carlson, Eric T. & Simpson, Meribeth M. **Opium as a tranquilizer.** American Journal of Psychiatry, 120:112-117, 1963.

Opium's place of origin, its uses, derivatives, and effects are explored, beginning with the Christian era through the late 19th century. It was used as a tranquilizer, for its effect as a hypnotic, and throughout the spectrum of psychiatric diagnoses for many centuries. It appears that the use of the drug as a tranquilizer started after 1832. In the 20 years that followed, its use in psychiatry reached a peak, with many doctors considering it the greatest pharmaceutical aid to psychiatry. Opium's addicting qualities had been noted from the earliest times. The gradual decline of enthusiasm for opium in the late 1880's was, in part, a response to the awareness of this addiction, which led to the use of cocaine and heroin, bromides, chloral hydrate, paraldehyde, ethyl sulfones, and barbiturates. Opium therapy in the 20th century has almost disappeared.

Cornell University Medical College
New York, New York

1085 Friend, Dale G. **Anti-parkinsonism drug therapy.** Clinical Pharmacology and Therapeutics, 4(6):815-822, 1963.

In this review, it is noted that Parkinson's disease is one of the most common neurological diseases. No definite etiological basis, however, has been established for it. Those in the very early stages of the disease and unable to have surgery can be benefited by a combination of physiotherapy and drug therapy. The drugs discussed here include scopolamine, biperiden, cycrimine, procyclidine, trihexyphenidyl, benztropine, ethopropazine, orphenadrine, diphenhydramine, and chlorphenoxamine. The structure and the cost per 100 tablets of each drug are given.

Peter Bent Brigham Hospital
Boston, Massachusetts

1086 Haas, Adolf. **Management of the geriatric psychiatric patient in a mental hospital.** Journal of the American Geriatrics Society, 11(3):259-265, 1963.

The problems of geriatric psychiatric patients are discussed, and the author's experience with a separate hospital unit for such patients is described. Recommendations are made for physical, hormonal, and psychotherapeutic management.

Ypsilanti State Hospital
Ypsilanti, Michigan

1087 Sargant, William. **Combining the antidepressant drugs.** (Letter) Lancet, 2(7316):1062, 1963.

The two groups of antidepressant drugs have been used together in numbers of cases, without any dangers that cannot usually be eliminated by proper adjustment of the dosage of each drug. Endogenous depressions, on the whole, were found to respond well to imipramine or amitriptyline. Certain groups of atypical or hysterical depressions and anxiety states in previously good personalities responded well to the monoamine oxidase inhibitor group of drugs.

St. Thomas's Hospital
London, S.E.1, England

1088 **Hypertensive crisis and monoamine oxidase inhibitors.** (Editorial) Canadian Medical Association Journal, 89:1149-1150, 1963.

Hypertensive crises have been reported most frequently with tranylcypromine, but they have occurred also in some patients taking phenelzine or other MAO inhibitors. Neither dosage nor duration of treatment appears to be related to their occurrence. The hypertensive reaction is characterized by a sudden onset of severe, throbbing, occipital and temporal headache, which later becomes generalized, and by an elevation in blood pressure. The incidence of this reaction is uncertain, varying from very small fractions of 1% to much higher percentages. The reaction may be accompanied by some or all of the following symptoms: neck stiffness, nausea and vomiting, sweating (with fever, or with cold, clammy skin), palpitations, photophobia, tachycardia or bradycardia, constricting chest pain, and dilated pupils. The clinical picture is often one of marked prostration, resembling pheochromocytoma or subarachnoid hemorrhage. The hypertension is usually short-lived. Intracranial bleeding or fatality in association with MAO inhibitor therapy, although uncommon, has been associated with other drugs that were being used as well, including iproniazid, amphetamine derivatives, ephedrine, and imipramine, and, in some cases, there was evidence of preexistent cerebral aneurysm. In some cases, no additional drugs had been given and no evidence of aneurysm was found. If a hypertensive reaction occurs, the MAO inhibitor should be discontinued; bed rest is indicated; and meperidine should not be given. Hypotensive agents may be used with caution, and other symptomatic and supportive measures may be desirable.

(No address)

1089 Feldman, Paul E. **Changing concepts. The somatic treatments in psychiatry: Current status.** Journal of the Kansas Medical Society, 64(1):11-12, 15, 1963.

Four groups of tranquilizers are listed: (1) chlorpromazine-like compounds (phenothiazine derivates); (2) reserpine compounds (Rauwolfia alkaloids); (3) diphenylmethane derivatives; and (4) glycerol derivatives. Tranquilizer therapy is being promoted on a major scale despite a host of side effects, including the following: (1) depression; (2) potentiation of action of other drugs; (3) masking of important alerting symptoms; (4) various gastrointestinal effects; (5) hepatic dysfunction; (6) cardiovascular effects; (7) various blood dyscrasias; (8) visual disturbances; (9) extrapyramidal effects; and (10) failure of respiratory defenses. Psychic energizers may be divided roughly into those which do and do not inhibit monoamine oxidase.

Topeka, Kansas

1090 Dickel, Herman A., Dixon, H. H., Shanklin, J. G., & Dixon, H. H., Jr. **Treatment of the tense, anxious, working patient.** General Practitioner, 27(4):136-139, 1963.

In the treatment of the tense, anxious, working patient, drugs are used as "crutches." The physician must learn the patient's response to various drugs so that the side effects will not interfere with work or health; the patient truly derives benefit from the drug; and improvement is not temporary or based on drug reliance. The drug used most often is meprobamate, in both regular and long-acting forms. It has proved to be realistically beneficial and reliable; it gives long-range assurance of little or no habituation; and it has few, if any, side effects.

University of Oregon Medical School
Portland, Oregon

1091 Kinross-Wright, John & Charalampous, K. D. **A psychopharmacology research unit.** Diseases of the Nervous System, 24: 299-301, 1963.

The operations of the Houston Psychopharmacology Center, an administrative and coordinating mechanism for a diverse group of

research units scattered over the state, are described. The Center is able to evaluate drugs from the level of animal pharmacology through to sophisticated controlled studies. The operating relationship among the Center's units are illustrated by describing the procedure used to evaluate fluphenazine enanthate, a short-chain fatty acid ester of a phenothiazine, fluphenazine. The Center provides focal point for clinical services and research laboratories to facilitate testing of new therapeutic drugs.

Baylor University College of Medicine
Houston, Texas

1092 Frank, Jerome D. **Neurosis.** In: Conn, Howard F., ed. Current Therapy. Philadelphia, W. B. Saunders, 1963, p. 535-539.

Approaches to the psychotherapy of neurotic distress are discussed. Support, information, emotional arousal, and retraining are proposed as sources of attitude change. Means of initiating and conducting therapy, the types of psychotherapy, ancillary methods, and group methods of treatment are among the topics covered.

The Johns Hopkins University
School of Medicine
Baltimore, Maryland

1093 Rosenberg, Stanton L. & Greaves, Donald C. **Schizophrenia.** In: Conn, Howard F., ed. Current Therapy. Philadelphia, W. B. Saunders, 1963, p. 550-553.

Treatment of schizophrenics by hospitalization, somatotherapies, and psychotherapy is discussed. The reasons for recommending hospitalization and circumstances governing the selection of the hospital and treatment methods are given. Of the various somatotherapies (EST, insulin shock, and psychotropic drugs), the use of psychotropic drugs is stressed. Proper treatment and maintenance doses of chlorpromazine, the drug of choice for treatment of acute schizophrenic reaction, are recommended. Side effects of chlorpromazine are listed. The psychotherapy of the schizophrenic, particularly the paranoid schizophrenic, is presented.

University of Kansas Medical Center
Kansas City, Kansas

1094 Hohman, Leslie B. **Psychoses: Mental depression.** In: Conn, Howard F., ed. Current Therapy. Philadelphia, W. B. Saunders, 1963, p. 548-550.

Symptoms of depression are divided into three categories and discussed in terms of the types of treatment possible---psychotherapy, psychoanalysis, and physical treatment.

Duke University
Durham, North Carolina

1095 Williams, John F. **The general practitioner and psychiatric drug treatment.** (Letter) Medical Journal of Australia, 1(16):611-612, 1962.

Iproniazid was prescribed by Dr. Williams for 3 years. In his experience, the toxicity, described in the literature, as shown by liver necrosis and unpleasant side effects has been grossly exaggerated. It appears that indiscriminate dosage may have been responsible for at least some of these unfavorable reports. Dr. Williams always prescribes iproniazid with pyridoxine, and considers iproniazid to be a valuable, though undoubtedly potentially toxic, drug that should not be discarded until a suitable substitute is found. Quite dramatic changes in personality and the disappearance of a wide variety of symptoms, including obsessive compulsive, phobic, and depressive, occur with the use of iproniazid.

12 Collins Street
Melbourne, Australia

1096 Prange, Arthur J., Jr. **Recent advances in therapeutics: Psychoactive drugs.** North Carolina Medical Journal, 24(2):63-66, 1963.

The renaissance of interest in drugs in the past 10 years has not decreased the number of hospitalized mental patients, but it has decreased hospitalization time and has changed attitudes about mental illness. The chief advance in this revival of interest is in the area of research, especially with the psychotomimetics. Through research, the biologic aspects of psychotic disorders may be investigated, and a more objective appraisal of new drugs is made that was not made with clinical studies. The following tranquilizers, each with a different chemical structure, are discussed: chlorpromazine, reserpine, meprobamate, benactyzine, and chlordiazepoxide (miscellaneous struc-

ture). The antidepressants phenelzine, tranylcypromine, imipramine, d-amphetamine, and pipradol (miscellaneous structure) are also presented. These latter drugs have reduced the use of EST. In conclusion, psychoactive drugs have increased the need for clinical judgment, experience, and caution.

University of North Carolina
Chapel Hill, North Carolina

1097 Mehta, Dilip J. **"Potency" and "efficacy" of drugs.** Journal of New Drugs, 3:12-14, 1963.

A hypothetical diagram, illustrating two assay methods, helps to explain the difference between potency and efficacy. To produce a 40% effect, doses of drugs X and Y are 20 units and 50 units, respectively. Drug X has, therefore, greater potency than Y. But, by using ceiling doses for comparison of the same drugs, X is found to have a 60% maximal effect (ceiling dose) and Y has a 90% maximal effect. In that case, drug Y has the greater efficacy. The "potency" assay method makes no indication as to which of the two drugs is preferable. A current method for the bioassay of diuretic agents compares the ceiling dose (the fixed element) of a standard with that of a test agent. The efficacy of the test drug is based upon the ratio of the maximal effect of the new agent to that of the standard. More practical information is obtained by using the efficacy assay than by using the potency method.

Hospital for Joint Diseases
New York, New York

1098 Kidd, H. B. **Drugs for depression.** (Letter: comment on letter by W. Sargant.) British Medical Journal, 1(5331): 681, 1963.

Dr. W. Sargant's letter on drugs for depression (February 9, p. 401) is criticized. The author states that Dr. Sargant's impression that the psychiatrists in psychiatric hospitals deal only with severe cases is wrong, as the majority of mental hospitals are doing work that is exactly comparable to the work of psychiatric units in general hospitals. Great benefit has been obtained from the use of antidepressant drugs in the treatment of depression, but the author emphasizes that the treatment of depression, particularly in estimating suicidal risk, should not be considered a simple matter of tablets.

The Towers Hospital
Humberstone, Leicester, England

1099 Jaeger, Philip. **Better nursing for the indigent aged.** Journal of the American Geriatrics Society, 11(8):797-800, 1963.

Nursing homes for the indigent aged are discussed in terms of the need for rehabilitation services, for better safeguards against accidents, and for better management of drug therapy. Financial problems and a lack of trained personnel are additional problems.

3584 Reading Road
Cincinnati, Ohio

1100 Bennett, A. E. **Anxiety as a symptom of mental illness.** General Practitioner, 27(5):101-106, 1963.

The causes and manifestations of anxiety are discussed. Errors in diagnosis, problems in treatment, and the use of drugs in the treatment of anxiety are among the other topics covered.

Herrick Memorial Hospital
Berkeley, California

1101 Popkin, Roy J. **Restless legs.** Journal of the American Geriatrics Society, 11(6):570-573, 1963.

The restless-legs syndrome, which was reintroduced to the profession in 1945, is reviewed. It consists of paresthesias and discomfort, including sensations of coldness, crawling, weakness, numbness, pain, "pins and needles," and burning in the legs. Specific etiologies proposed by investigators have varied---neurologic, vasomotor, or neurovascular causes have been suggested. The writer's opinion, however, is that venous stasis is a causative factor. Many arguments are given to substantiate this belief. The many diverse pharmacological treatments and preventive measures recommended are listed. It is concluded that measures to prevent venous stasis also aid in preventing and relieving symptoms of this syndrome.

6423 Wilshire Boulevard
Los Angeles 48, California

1102 Longmire, Warren T., Jr. & Davis, Harry K. **Acute imipramine intoxication.** American Journal of Psychiatry, 120: 400-402, 1963.

The literature concerning imipramine intoxication is reviewed. A case study describes a 44-year-old female patient who ingested 2,325 mg of imipramine and who had no medical treatment for 8 hours. On admission, the patient was comatose, respiration was shallow and irregular, and no blood pressure or pulse was obtainable. Chest X-ray showed a bilateral diffuse infiltration in both lung bases. Initial treatment was mainly supportive; it included nasal oxygen, i.v. dextrose in distilled water with vasopressors added, and antibiotics. After 6 hours of the supportive treatment, blood pressure and pulse stabilized and rigidity and clonus disappeared. The patient was discharged after 3 days and was assigned to the outpatient psychiatric clinic.

University of Texas Medical Branch
Galveston, Texas

1103 Jenner, F. A. **Attempts to explain the mode of action of some drugs of value in psychiatry.** Anglo German Medical Review, 1:437-447, 1962.

A discussion is given of the monoamines, adrenaline, noradrenaline, dopamine, and 5HT, and their actions in specific sites of the brain. It is stated that the remarkable achievement of modern psychopharmacology and biochemistry lies in their creation of sophisticated hypotheses that are ultimately testable. It is concluded that psychopharmacology is bringing us closer to a biochemical basis for some aspects of mental disorders and functions.

Woofindin Road
Sheffield 10, England

1104 Freedman, D. X. & Giarman, N. J. **Brain amines, electrical activity, and behavior.** In: EEG and behavior. New York, Basic Books, 1963, p. 198-243.

This review of the relationship of amines to neural function and behavior proposes to give the basis for some of the ongoing research, and to orient the nonspecialist to some of the conceptual pitfalls, methodologic problems, and substantive gaps that can be found. Major emphasis is placed on 5HT. The neurohumoral role of amines and problems in evaluating that role are discussed. There is also a section concerning brain amine, in which a table is given of the distribution of 5HT in brain regions. Three other main topics are included: (1) Methods for Manipulating Amine Mechanisms---transport of precursor, synthesis of amine, release of amine, selective and blocking release, inhibition of destruction, receptor sites, and brain amines in man; (2) Neurohumoral Role of Serotonin; and (3) EEG and Behavioral Effects---effects on evoked potentials, EEG and behavioral effects of 5HTP, MAO inhibitors, LSD-25, reserpine, and effects of altered amine mechanisms. Figures are included of mechanisms governing brain-amine levels and the tolerance of LSD-25 to behavioral and EEG effects. (176 references)

(No address)

1105 Levy, Leonard & Ban, Thomas. **Phenothiazine drugs and the general practitioner.** Canadian Medical Association Journal, 86:415-417, 1962.

The phenothiazines are historically surveyed, and a classification relating therapeutic indications to chemical structure is proposed. Clinical applications and the selection of appropriate drugs for treatment of psychiatric disorders are discussed. A table presents the generic name, trade name, daily dosage, efficacy, and complications of 14 frequently used phenothiazines.

McGill University
Montreal, Canada

1106 **Deserpidine (11-demethoxyreserpidine).** British Medical Journal, 2(5307):793, 1962.

In the section called "To-day's Drugs," deserpidine, an alkaloid derivative of Rauwolfia canescens, is discussed. Its chemistry, pharmacology, toxicity, clinical use, and dosage and administration are outlined.

(No address)

1107 Jacobziner, Harold. **Poisonings associated with tranquilizers.** Clinical Pediatrics, 1:16-18, 1962.

At least 35 different tranquilizers are in current use, sometimes without valid reason and with questionable therapeutic effect. In

this review, a table is given that lists 94 accidental poisonings from 70 poisonous agents reported to the New York City Poison Control during a typical weekend, to illustrate the increasing danger. Adverse side effects from various classes of drugs are discussed in general. A more detailed background of thalidomide is also given. The article concludes with the warning that extreme caution must be exercised when administering drugs, especially to pregnant women.

New York City, New York

1108 Dalessio, Donald J. **Recent experimental studies on headache.** (Paper presented at the Fourteenth Annual Meeting of the American Academy of Neurology, New York City, April 28, 1962. Symposium on Headache: Its Mechanism, Diagnosis, and Management.) Neurology, 13(3):7-10, 1963.

The structure of methysergide is briefly discussed, and its effects on blood vessels are described. It is concluded that methysergide acts centrally by modulating central vasomotor functions and peripherally by potentiating the vasoconstrictor responses of the cranial blood vessels to catecholamines.

(No address)

1109 **Pargyline: Novel monoamine oxidase inhibitor.** Texas State Journal of Medicine, 58:190, 1962.

The literature pertaining to pargyline is reviewed, with emphasis on two reports of major significance. These are the studies of Bucci and Sanders on the antidepressive properties of pargyline and the studies of Ford on its effects on blood pressure. Other reports are also cited, especially those concerning structure--activity relationships. (7 references)

(No address)

1110 Delgado, Jaime N. & Worrell, Lee F. **Versidyne: A new analgesic.** Texas State Journal of Medicine, 58:190-191, 1962.

Versidyne (Ro 4-1778/1), a tetrahydroisoquinoline derivative, is briefly compared with other analgesics. It is indicated that Ro 4-1778/1 does not fit into any of the standard classifications of analgesic agents.

College of Pharmacy
University of Texas
Austin, Texas

1111 Moyer, John H., Brest, Albert N., & Nathanson, Donald. **Medical consideration in the hypertensive patient undergoing surgery.** American Journal of Cardiology, 12: 286-292, 1963.

Three categories of medical considerations are discussed: (1) the influence of hypertension on the patient's condition; (2) the effect of the surgical procedure on the hypertension; and (3) those special considerations which relate to antihypertensive drug therapy. The effect of diuretics and sympathetic depressants, such as the Rauwolfia compounds, guanethidine, and ganglionic blocking agents, on the surgical status of the hypertensive patient is described in detail.

Hahnemann Medical College
Philadelphia, Pennsylvania

1112 DiPalma, Joseph R. **Problems of drug reactions.** American Journal of Cardiology, 12:349-353, 1963.

The multiplicity of drugs now used with the patient who undergoes surgery has disadvantages not anticipated when the single therapeutic aim of each drug alone is considered. The chances of additive, synergistic, and potentiating effects are increased. The types of undesirable drug reactions discussed are as follows: allergic reactions causing symptoms of anaphylaxis; side reactions (gastrointestinal, circulatory, respiratory, and neuromuscular); and specific drug reactions from anticoagulants, insulin, digitalis, blood transfusions, local anesthetics, and posterior pituitary preparations. A table of drugs that may be used in the average operation is given; they are grouped as preanesthetics, prophylactics and therapeutics, anesthetics, special-purpose drugs, and postoperative drugs. Each drug that is added to the therapy of the surgical patient must be considered not only in regard to its toxic effect but also in relation to all the effects of the other drugs being used.

Hahnemann Medical College and Hospital
Philadelphia, Pennsylvania

1113 Rodman, Theodore. **The effect of anesthesia and surgery on pulmonary and cardiac function.** American Journal of Cardiology, 11:444-450, 1963.

In this review, it is stated that preoperative medication, anesthesia, assisted ventilation, and surgery are all potentially detrimental to pulmonary and cardiac function. Ten mechanisms of cardiopulmonary function adversely affected by anesthesia and surgery are listed. The factors affecting pulmonary function, i.e., preoperative medication, anesthetics, body position, etc., are described. Four figures are included that show the effect of oxymorphone on the ventilatory response to increases of carbon dioxide, respiratory depression from oxymorphone in a patient with emphysema, the effect of nitrous oxide and thiopental on ventilatory response to carbon dioxide, and the effect of lateral position on pulmonary ventilation and pulmonary capillary blood flow. The factors affecting cardiovascular function, anesthesia and assisted ventilation, are also described, and figures of the effect of cyclopropane anesthesia on myocardial contractility and effect of positive intrathoracic pressure on cardiac output are also shown. Clinical implications, especially in relation to the patient with pulmonary emphysema, are given.

Veterans Administration Hospital
Philadelphia, Pennsylvania

1114 Hammett, Van Buren O. **Psychiatric complications of surgery.** American Journal of Cardiology, 12:477-479, 1963.

In this review of preoperative and postoperative psychiatric complications, only those occurring most frequently in relation to the surgical situation are discussed. These are, in order of frequency, the anxiety reaction, depression, denial of illness, and the acute brain syndrome. Each complication is defined and described, including its signs, symptoms, and management. Therapy is based on the institution of on-the-spot psychotherapy plus adjunctive drug therapy.

Hahnemann Medical College and Hospital
Philadelphia, Pennsylvania

1115 Hand, B. Marvin & Nathanson, Donald L. **Neurologic complications following cardiac surgery.** American Journal of Cardiology, 12:480-481, 1963.

Although they occur infrequently, two types of severe complications may follow cardiac surgery---neurologic conditions (embolism and hypoxic encephalopathy), in which abnormal physical signs, such as clouding of consciousness, altered reflexes, disturbances of sensation, cranial-nerve abnormalities, and motor weakness or paralysis can be seen; and psychiatric conditions, in which emotional disturbances, delusional trends, hallucinations, or other disturbances of thinking and affect are apparent without evidence of organic brain damage. These two complications are discussed, and three illustrative cases are presented.

Hahnemann Medical College and Hospital
Philadelphia, Pennsylvania

1116 Catenacci, Alfred J. **The physiology and therapy of anesthetic shock.** American Journal of Cardiology, 12:595-598, 1963.

In this review, the physiology of anesthetic shock, whereby the circulation and respiration are depressed, is discussed in detail. In low concentrations, anesthetics produce minimal effects; in large concentrations, vital functions are dangerously depressed. The following topics as related to anesthetic shock from various agents or methods are described: premedication interferences, inhalation agents, cyclopropane, diethyl ether, i.v. anesthetics, spinal shock, and procaine shock. In the management of anesthetic shock, a correct diagnosis is required before therapy, the patient's physical history must be known, and the surgeon and anesthesiologist must be aware of their responsibilities. In conclusion, shock is corrected through early recognition and through removal of the anesthetic by hyperventilation with oxygen.

Hahnemann Medical College and Hospital
Philadelphia, Pennsylvania

1117 Nickerson, Mark. **Sympathetic blockade in the therapy of shock.** American Journal of Cardiology, 12:619-623, 1963.

Laboratory and clinical observations have been presented to show that vasoconstriction in response to hyperactivity of the sympathetic nervous system may play a deleterious role in the development of shock. Most accepted clinical signs of shock are also signs of vasoconstriction. Many procedures and drugs that inhibit vasoconstriction or induce vasodilation increase survival, as shown by

experiments using induced shock. Phenoxybenzamine has a beneficial effect in various types of shock, and, in addition, it provides a simple and reliable measure of the adequacy of prior therapy with blood and other fluids, and allows the rapid administration of larger amounts of i.v. fluids in patients with myocardial inadequacy. The topics discussed include the role of vasoconstriction in the development of shock, inhibition of sympathetic vasoconstriction, and clinical results of dibenzyline therapy. Figures are given of the course of shock in two patients.

University of Manitoba Faculty of Medicine
Winnipeg, Manitoba, Canada

1118 Morse, Dryden P. **The management of shock in cardiac surgery.** American Journal of Cardiology, 12:624-627, 1963.

In addition to the problems of shock in general surgery, cardiac surgery encompasses several additional complicating elements. These are, primarily, a diseased heart or an inadequate blood volume and, secondarily, the effects of anesthetics that may cause peripheral dilatation or deterioration of the myocardial contraction, the effect of intracardiac surgery itself, and the effects of anoxia or acidosis. Some of these factors leading to shock are described, and their treatment and prevention are outlined. The problems are considered in terms of: (1) prevention of shock by preoperative measures; (2) the types of operative shock---hemorrhagic, anesthetic, and myocardial; and (3) the types of postoperative shock---shock during chest closure, cardiac arrhythmias, hypoventilation and hyperventilation, and vasopressors. Proper insight concerning cardiac shock can result in effective treatment or, in many cases, in prevention.

Hahnemann Hospital and Medical School
Philadelphia, Pennsylvania

1119 Abrams, William B., Moe, Robert A., Bates, Harold, Wallen, Marvin, Odze, Melvin, Crews, Asa, & Pocelinko, Robert. **Adrenergic mechanisms in the treatment of essential hypertension.** American Journal of Cardiology, 12:711-720, 1965.

The desire for specificity of action had brought about special interest in antihypertensive drugs that act principally at the sympathetic arteriolar site and/or on norepinephrine, the neurohumoral transmitting agent. This report gives pharmacological and clinical studies on three of these drugs: reserpine, guanethidine, and bretylium. Their mechanisms of action in lowering blood pressure and how the identification of these mechanisms altered long-established physiological concepts of the efferent sympathetic nervous system are discussed. The pharmacology of the efferent sympathetic nervous system is also given. These studies indicate that although many agents exert their major effects at the sympathetic neuroeffector site, the precise actions are not necessarily identical. As a result, new approaches have been opened for the medicinal chemists to provide us with better agents for the control of blood pressure. (17 figures and 41 references)

Hoffmann-La Roche, Inc.
Nutley, New Jersey

1120 Katz, Martin M. & Cole, Jonathan O. **Research on drugs and community care. A review and analysis of recent results and methodological progress.** Archives of General Psychiatry, 7(11):345-359, 1962.

The proceedings of a research conference on drugs and community care are summarized. Six research projects are reviewed: (1) home versus hospital care for schizophrenics; (2) ataractics in outpatient schizophrenics; (3) drug therapy in a day-care facility for relapse control; (4) termination of treatment with ataractic drugs; (5) drugs and social therapy in chronic schizophrenia; and (6) effect of ataractic drugs on hospital-release rates. Papers on predictor variables (including clinical history, sociological variables, and the role of personality), data collection and analysis, and methods for measuring improvement are also reviewed. A summary of the more important clinical results reported in conference papers, as well as problems in meeting requirements of research design are discussed. Recommendations are made on methodological issues that grew out of the conference discussions.

National Institute of Mental Health
Bethesda, Maryland

1121 Peppel, H. H. & Joynes, T. **Study design for clinical evaluation of phenothiazine derivatives.** American Journal of Psychiatry, 120:497-499, 1963.

A short, clinical screening procedure was devised for quickly assessing the value of new phenothiazine compounds in treating

schizophrenia. The 3-month controlled trial embraces only patients stubbornly resistant to treatment. A special rating scale was devised that differentiates among the various common drug actions, with chlorpromazine as the standard. Carphenazine maleate was the first drug tested. In doses up to, but not exceeding, 150 mg/day, carphenazine is superior to chlorpromazine in ability to influence mood, physical and mental activity, and degree of hostility and tension. Carphenazine is recommended for use in chronic schizophrenia when other therapies fail.

Hawthornden State Hospital
Macedonia, Ohio

1122 Alexander, Leo & Cass, Leo J. **Profiling as an aspect of psychiatric diagnosis with reference to the matching of control groups for the study of drug effects.** American Journal of Psychiatry, 120:387-389, 1963.

A profiling method was devised for the evaluation of differential effects of treatment in patients falling into otherwise identical diagnostic categories. The clinical profile consists of the following eight specifications: (1) ability to work; (2) participation in home and social activities; (3) depressive issue; (4) state of ego function; (5) ability to communicate; (6) psychomotor responsiveness; (7) objectivity; and (8) sleep pattern. Four grades of functions are scored for each specification, ranging from normal to increasingly severely distributed functions. The use of this method for matching treatment and control groups is recommended.

Tufts University Medical School
Boston, Massachusetts

1123 Friedlander, Walter J. **Epilepsy.** American Journal of Psychiatry, 119: 654-659, 1963.

A review of current literature on epilepsy is given. Studies on the parameters of electrical stimulation and the characteristics of a seizure are described. References that discuss the relation between seizures and maturation, the influence of genetic factors, and a variety of birth defects, organic lesions, endocrine malfunctions, and bacterial and viral infections leading to epileptic seizures are presented. Reports on the effects of alcohol on seizure threshold are noted. The testing of anticonvulsant drugs is reported. The occurrence of psychoses in epileptics is reviewed. (132 references)

Albany Medical College
Albany, New York

1124 Wittenborn, J. R., Maurer, Helen, & Plante, Marc. **Methods for treating depression evaluated after the elapse of one year.** Journal of Nervous and Mental Disease, 136(5):492-499, 1963.

A portion of a continuing study of the relative efficacy of iproniazid, ECT, and placebo in the treatment of mental-hospital patients suffering from a depression is described. About one year after the completion of hospital treatment, a social worker visited the homes of the patients to gather specific information concerning the patients' circumstances, attitudes, behavior, and general welfare. The three treatment groups are compared with respect to these items of information.

Rutgers-The State University
New Brunswick, New Jersey

1125 Karliner, William. **ECT or Indoklon: Comment.** Journal of Nervous and Mental Disease, 136(6):597-598, 1963.

A comment is made on a paper by Sandifer, Albert, and Wilson (J Nerv Ment Dis, February 1962) that stated that depressed female patients preferred EST to Indoklon therapy. The statement was based on 14 EST and 14 Indoklon therapy. The results are questioned since the patient sample was so small, and the Indoklon treatment method employed was neither the safest nor the most effective one in use. The improved Indoklon treatment method is discussed. Results from 1,500 Indoklon treatments show that most patients prefer Indoklon to EST.

1749 Grand Concourse
Bronx, New York

1126 Spiegel, Herbert & Shainess, Natalie. **Operational spectrum of psychotherapeutic process.** Archives of General Psychiatry, 9:477-488, 1963.

There are four dissonant areas in the broad field of psychiatric therapy: (1) conflicting appraisals of psychotherapeutic effec-

tiveness; (2) the confusing interchange of therapy goals with research goals; (3) classical nosology; and (4) therapeutic chauvinism. To cope with these problems, a theoretical framework is proposed that acknowledges that patients respond to a variety of therapeutic approaches; gives primacy to treatment goals, even if they conflict with research design; categorizes clinical syndromes on a practical operational continuum, using special data in determining the most appropriate treatment mode; and enables more precise communication between therapists and patients. The computer paradigm of input--output helps to clarify the initial task of the therapist in processing data. To implement this, theoretical concepts of Myth--Belief Constellation and process were developed briefly and defined. Also discussed are implications of consonance and feedback between the two, as well as range and shift with therapy. An operational approach is offered that makes possible a quick grasp of the psychodynamic issues in relation to a spectrum comprising eight major clinical categories, which, in turn, facilitates selection of the appropriate therapeutic approach.

Columbia University
New York, New York

1127 Regan, Peter F. **Psychoses: Manic-depressive reactions.** In: Conn, Howard F., ed. Current Therapy. Philadelphia, W. B. Saunders, 1963, p. 539-543.

An approach to the treatment of depressive and manic episodes is outlined. The following topics are included: protection of the patient, activity program, psychotherapeutic program, and physical treatments.

University of Florida
Gainesville, Florida

1128 Smith, Jackson A., Willrich, Karl, & Rudy, Lester H. **Choice of psychoactive drugs by psychiatric residents.** Diseases of the Nervous System, 24(5):310-313, 1963.

To determine which of the many psychoactive drugs were preferred and what might influence the choice of a particular psychoactive drug, 38 psychiatric residents were asked to state their preferences on a questionnaire. The following information was asked: (1) first and second choice of phenothiazine derivatives and nonphenothiazines prescribed as tranquilizers for inpatients; (2) choice of medication for four diagnostic groups; (3) duration of treatment with a drug if the patient responded and if he failed to respond; and (4) the two major sources of information about drugs. The group appeared to choose psychoactive drugs according to presumed effectiveness, medical advertising, and suggestions from the senior staff.

Illinois State Psychiatric Institute
Chicago, Illinois

1129 Mandell, Arnold J. **The psychologic management of coronary patients.** General Practitioner, 27(1):82-91, 1963.

Psychologic factors in cardiovascular disease, especially coronary artery disease, are discussed. Common psychologic responses are mild to severe depression, marked hypochondriasis, and denial of illness. The concept of a "coronary personality," i.e., definite patterns of personality dysfunction statistically associated with the incidence of this disease, is introduced. In addition to these subjects, the following are discussed with respect to cardiovascular disease: the clinical picture; critical areas of patient management (patient--doctor relationship); activity, passivity, and self-esteem; alternative activities; sexual activity; impotence; and psychotropic drugs.

University of California Medical Center
Los Angeles, California

1130 Poser, Charles M. **Management of patients with vascular or migraine headaches.** General Practitioner, 27(6)122-130, 1963.

The definition, classification, mechanism of action, and differential diagnosis of migraine headaches are presented. Provocative and predisposing elements, such as heredity, psychological factors, physical factors, and epileptic cephalea, are discussed. Treatment of migraine is described in detail. Patients are divided into two groups---those with recognizable auras or prodromata at least 20 minutes before an attack, and those without preheadache auras. For patients with an aura, ergotamine---a powerful vasoconstrictor---is given at the first manifestation of aura. Various commercial ergotamine preparations are recommended, and effective dosages are given. For patients without aura, the potent vasodilator methysergide in doses of one 2-mg tablet t.i.d. is recommended. If the migraine attacks do not occur in a recognizable pattern, methy-

sergide must be taken indefinitely. Treatments for actual migraine attack and the migrainoid state are suggested. Complications that may arise from the use of ergotamine or methysergide are discussed.

University of Kansas School of Medicine
Kansas City, Kansas

1131 Maholick, Leonard T. **The discharged mental hospital patient.** General Practitioner, 28(4):116-120, 1963.

The role of the family physician in rehabilitating former mental patients is described. The following areas are discussed: (1) the development of a system for collecting the maximum amount of personal data in the minimum amount of time; (2) the values and limitations of therapeutic talking time; (3) the significance of interviewing and its scheduling; (4) the uses and abuses of psychotropic durgs; (5) the extent of community resources; and (6) the development of a consulting relationship with an acceptable psychiatrist.

The Bradley Center, Inc.
Columbus, Georgia

1132 Ruesch, Jurgen, Brodsky, Carroll, & Fischer, Ames. **The acute nervous breakdown.** Archives of General Psychiatry, 8:197-207, 1963.

A description of a combination of psychological, social, and somatic procedures used on a psychiatric service dedicated to the management of acute conditions is presented. The elements of the treatment program are action therapy, relational therapy, social engineering, interpretative psychotherapy, drugs, and electroshock treatment. The four major syndromes considered are depressions, schizophrenic disorders, psychoneurotic and characterological disorders, and acute and chronic brain disorders.

University of California School of Medicine
San Francisco, California

1133 Carr, C. Jelleff. **An appraisal of animal drug screening techniques used in psychopharmacology.** Journal of New Drugs, 3(3):135-146, 1963.

The published literature on animal behavioral techniques used to test psychopharmacological agents of known merit is reviewed. Three classes of animal behavioral methods are presented: (1) changes in unlearned behavior; (2) changes in learned behavior; and (3) evaluation of natural responses to environmental stimuli, using a rating scale. Animal behavior tests involving unlearned behavior (unstimulated and stimulated motor activity), potentiation measures, and drug effects on specific behavior patterns in animals are discussed in detail. The problems in extrapolating data from animal studies to "abnormal" man are described. (75 references)

Army Research Office
Arlington, Virginia

1134 Venning, G. R. **A hypothesis concerning a site of action of tranquilizing drugs and the significance of associated extrapyramidal motor phenomena.** Journal of New Drugs, 3(6):351-355, 1963.

Research concerning the significance of drug-induced extrapyramidal phenomena is reviewed. It is proposed that the tranquilizing action of neuroleptic drugs upon behavior may be partly mediated through the inhibitory function of the extrapyramidal system.

G. D. Searle and Co., Ltd.
High Wycombe, England

1135 McHardy, Gordon, Balart, Louis, Craighead, Claude C., McHardy, Robert, & Ward, Swan. **Geriatric gastrointestinal therapy, including observations on the effect of dicyclomine.** Journal of the American Geriatrics Society, 11(3):199-210, 1963.

Geriatric gastrointestinal therapy is discussed under the following categories: general measures, diet, antibiotics, sedatives, antacids, antispasmodics, blood transfusions, and surgical treatment. The response of 500 gastroenterologic patients treated with dicyclomine is reported. All but 12 patients reported complete or satisfactory relief; 47 patients noted side effects, including fatigue, vertigo, drowsiness, and dryness of mouth.

Louisiana State University School of Medicine

1136 Salzberger, Gideon J. **Combined chlorpromazine and trifluoperazine on a readmission service.** Diseases of the Nervous System, 24(9):558-561, 1963.

The successful use of combined chlorpromazine and trifluoperazine in treating readmitted psychotic patients is reported. One-

hundred male patients, 18 to 58 years of age, were treated with the following dose regimen: 150 mg chlorpromazine i.m. or 100 mg chlorpromazine combined with 5 mg trifluoperazine i.m. on admission, followed 2 or 3 hours later by 150 mg chlorpromazine together with 4 mg trifluoperazine p.o. t.i.d. Of the 100 patients, 75 were controlled enough by the combination of the two drugs to be released to open wards. The combination had two advantages over chlorpromazine alone. In combination, the dosage of chlorpromazine could be reduced from the usual 300 to 700 mg t.i.d. to 150 mg t.i.d., thus reducing the incidence of side effects. Chlorpromazine alone required 3 to 4 weeks to exert its effect, but the combination usually controlled the patient's symptoms within 7 to 10 days. Three case histories of patients treated with the combination are given. The drug combination is a rapid, effective means of controlling acutely agitated patients with marked hallucinations and delusions.

Pilgrim State Hospital
West Brentwood, New York

1137 Rosati, D. **Prolonged high dosage medication in chronic schizophrenia.** Diseases of the Nervous System, 24(11):683-687, 1963.

A standardized method for the treatment of chronic schizophrenics is presented. The method consists of four stages of medication, which are described in full: (1) adequate high dosage---initial treatment with very high doses (up to 400 q.i.d.) of chlorpromazine or equivalent phenothiazine; (2) therapeutic stage---dosage is one-fourth lower than the first stage; (3) maintenance dosage and training for discharge---dosage is lowered to one-half the initial dosage; and (4) maintenance medication and discharge---dosage is never lower than 400 mg chlorpromazine or higher than 800 mg chlorpromazine (or its equivalent). Antiparkinsonism drugs are given concurrently to minimize extrapyramidal side effects. Dosage is not fluctuated during any stage. In cases of hypotensive effects, medication is stopped for a few days, but dosage is not lowered. Of 55 male patients treated on the above regimen, 26 were discharged.

Veterans' Administration Hospital
Pittsburgh, Pennsylvania

1138 Dorfman, Wilfred. **Recent advances in psychopharmacology.** Diseases of the Nervous System, 24(11):694-697, 1963.

To further a better understanding of psychodynamics below the conscious level and of differential diagnosis in connection with prescription of the newer psychopharmaceutical agents, differences between types of depression and the possible roles of specific psychopharmacological agents in the management of these depressions are discussed. The types of depression discussed include: reactive depression; endogenous depression; manic-depressive depression; involutional depression; senile depression; schizoaffective disorders combining the features of schizophrenia with those of depression; depressive equivalents including somatic symptoms with or without somatic disease; somatopsychic depression; and iatrogenic depression following surgery and following the use of drugs (both biochemical and psychodynamic effects). It is emphasized that, in anxiety-tension states, attempts should be made to determine the etiology of the anxiety. Drugs that can be used in nonpsychotic states are also discussed.

1921 Newkirk Avenue
Brooklyn 26, New York

1139 Michaux, Mary Helen & Kurland, Albert A. **Combined psychotropic drug therapy.** Diseases of the Nervous System, 24(12):739-741, 1963.

The results of a survey in which doctors at three state hospitals were asked to report their experiences with combinations of psychotropic drugs are presented. The doctors were questioned about preferred sequence of administration, dosages, and types of patients to whom drug combinations are given.

Spring Grove State Hospital
Baltimore, Maryland

1140 Goldsmith, Jewett & Drye, Robert C. **Milieu as a variable clinical drug research.** Diseases of the Nervous System, 24(12):742-745, 1963.

A study that began as a double-blind evaluation of phenelzine in the treatment of depression is discussed in terms of the milieu in which it was conducted. Previous work on this subject is reviewed.

Illinois State Psychiatric Institute
Chicago, Illinois

1141 Hagopian, Peter B. & Crossfield, Ruth M. **Experiences with chlorprothixene in a state hospital.** Diseases of the Nervous System, 24(6):353-356, 1963.

A series of 168 female patients under active therapy with chlorprothixene was studied. Most of the patients were in the age range of 21 to 80 years and were on continuous chlorprothixene therapy for 1 to 24 months. All patients exhibited hyperactivity, agitation, or insomnia. Psychiatric diagnoses were varied. The most frequent initial chlorprothixene dosage was 150 mg daily; the maintenance dose was usually 100 or 150 mg daily (range, 15 to 900 mg daily). Marked or moderate beneficial response to chlorprothixene therapy was observed in 115 patients (including 37 of 53 with schizophrenia, 17 of 19 with depression, and 15 of 25 with arteriosclerosis or chronic brain syndrome). Drowsiness was the most frequent side effect, but was not considered to be a disadvantage. A few cases of mild hypotension were noted.

Danvers State Hospital
Hathorne, Massachusetts

1142 Patel, Natoo, Mock, David C., Colmore, John P., & Clark, Mervin. **A comparative clinical study of methylclothiazide and pargyline in patients with essential hypertension.** Clinical Pharmacology and Therapeutics, 4(6):740-748, 1963.

A group of 21 males and 7 females with essential hypertension of moderate severity was divided into four matched study groups for a double-blind comparison of pargyline hydrochloride, methyclothiazide, pargyline-methyclothiazide, and placebo. The average duration of known hypertension was about 9 years. The study was divided into three periods: 12 weeks of control observation, 4 weeks of placebo, and 18 weeks of drug administration. Group I received one 5-mg methyclothiazide tablet and one placebo tablet daily. By the final two weeks of the study, dosage was one methyclothiazide and five placebo tablets daily. Group II received one 25-mg pargyline tablet and one placebo tablet daily. Pargyline dosage was increased by 25 mg during each successive 2-week period. Dosage was eventually stabilized at 50 mg of pargyline. Group III received 5 mg of methyclothiazide daily plus pargyline in the same number to match the schedules of the other groups. The largest drop in blood pressure occurred consistently in the group receiving the drug-combination. This group, initially, had the highest incidence of side effects (dizziness, nightmares, fainting, nervousness, insomnia, and weakness), but these were obviated without loss of therapeutic effect when the pargyline dose was reduced. The hypotensive effects of either drug given alone did not differ significantly from that of the placebo.

University of Oklahoma School of Medicine
Oklahoma City, Oklahoma

1143 Hollister, Leo E., Kanter, Saul L., & Clyde, Dean J. **Studies of prolonged-action medication. III. Pentobarbital sodium in prolonged-action form compared with convential capsules: Serum levels of drug and clinical effects following acute doses.** Clinical Pharmacology and Therapeutics, 4(5): 612-618, 1963.

Twelve volunteer subjects each received four 200 mg doses of pentobarbital sodium, two doses in the prolonged-action form and two doses as conventional capsules. Intervals of 1 week separated each dose. The subjective responses of the subjects were measured by the Clyde Mood scale administered at 2, 4, and 8 hours after the drug. Determinations of serum levels of pentobarbital sodium were made at 2, 4, 8, and 24 hours following the acute dose of the drug. A modification of the existing technique for fluorometric analysis of pentobarbital in serum was developed. Mean serum levels of pentobarbital following the capsules were significantly greater than from the prolonged-action medication at 2 hours. First trials of the capsules showed significantly higher levels of the drug than second trials at 4, 8 and 24 hours. No significant differences were found between successive trials of prolonged-action medications. Global estimates of the effects indicated that, for most subjects, the capsule dose had greater intensity and duration. Capsules appeared to have more effect as determined by the Clyde Mood scale at 2 and 4 hours, but less at 8 hours.

Veterans Administration Hospital
Palo Alto, California

1144 Braunwald, Eugene, Chidsey, Charles A., Mason, Dean T., & Morrow, Andrew G. **Effects of reserpine and of congestive heart failure on the myocardial norepinephrine concentration in man.** (Paper presented at the 76th Session of the American Association of Physicians, Atlantic City, April 30-May 1, 1963.) Transactions of the American Association of Physicians, 76:254-261, 1963.

The right or left atrial appendage was excised in 51 patients undergoing open cardiac operation, and the norepinephrine contents were analyzed by the trihydroxyindole method. None of the patients had suffered from chronic congestive heart failure, and none had received a pressor agent prior to biopsy. Five adult patients were treated with a total reserpine dose of 16 to 25 mg over a period of 38 to 68 days. The norepinephrine concentration in the artial appendages of the control patients ranged from 0.63µg/g to 3.58µg/g of tissue; in reserpine-treated patients the range was 0.04µg/g to 0.36µg/g. Four of the patients who received reserpine were subjected to further tests. It was found that the maximum post-Valsalva overshoot was diminished following reserpine, that the absolute level of forearm vascular resistance during the cold pressor test was always lower than the level prior to reserpine, and that a reflex increase in venous tone was abolished or strikingly reduced by reserpine treatment. These effects disappeared several weeks after the discontinuation of reserpine. The myocardial norepinephrine concentrations in 17 patients who had suffered from congestive heart failure for more than 1 year ranged from 0.08µg/g to 1.64µg/g of tissue.

National Heart Institute
Bethesda, Maryland

1145 Hsu, John J., Braun, Robert A., Domino, Edward F., Lowinger, Paul, Schorer, Calvin, & Bruck, Morris. **Clinical evaluation of hydroxyphenamate in psychotic patients.** Diseases of the Nervous System, 24(12):1-2, 1963.

Twenty chronically disturbed, female inpatients (18 to 55 years of age) were used in a double-blind evaluation of hydroxyphenamate. The group consisted of 18 schizophrenics and 2 patients with chronic organic brain disease. Nineteen of the patients had been on phenothiazines for at least 2 months prior to the study; one patient had been on chlordiazepoxide. The study was conducted over three 2-week periods. All psychotropic drugs were abruptly discontinued. During the first 2 weeks, all patients received a chlorpromazine placebo. Ten patients were then given hydroxyphenamate and 10 received placebo. During the last 2-week period, medication for these two groups was reversed. Actual daily drug dosage ranged from 800 to 3,200 mg. The Ferguson Hospital Adjustment Scale and the Physician's Rating Scale were used to evaluate mental status. Hydroxyphenamate did not improve behavior more effective than placebo in relieving anxiety. Hydroxyphenamate, at the higher doses, tended to produce fast waves in the EEG's of the patients.

Pontiac State Hospital
Pontiac, Michigan

1146 Freedman, Daniel X. & Benton, Arnold J. **Persisting effects of reserpine in man.** New England Journal of Medicine, 264:529-533, 1961.

The recovery curves of blood values of serotonin and pupil size were determined in a group of 14 female patients (aged 26 to 55 years) with chronic schizophrenia after single large doses of reserpine. They had a mean hospital duration of 12 years, and none had been on reserpine for at least 2 years prior to the study. All other medications were discontinued at least 1 month before the study began. A single dose of 10 mg of reserpine was administered orally. Blood level of serotonin was measured at intervals. Five weeks after the first dose, a second 10 mg dose of reserpine was given. Blood levels were again measured, and pupil size was determined. After each 10 mg dose, the majority of patients became ill, with vomiting, diarrhea, insomnia, weakness, lassitude, drowsiness, depression, and psychomotor irritability being the symptoms most commonly observed. These subsided within 24 hours. Blood serotonin returned to normal in 5 weeks and pupil size in 7 days. After the second reserpine dose, a 5-week period was necessary for the recovery of both blood serotonin and pupil size.

Yale University School of Medicine
New Haven, Connecticut

1147 O'Brien, Donough & Jensen, Charlotte B. **Pyridoxine dependency in two mentally retarded subjects.** Clinical Science, 24:179-186, 1963.

Case reports describe two young, mentally retarded women with no history of convulsions who were found to have an impairment of the

pyridoxine-dependent kynureninase reaction as judged by xanthurenic aciduria and an elevated urinary hydroxykynurenine-hydroxyanthranilic acid ratio after an oral tryptophan load. No evidence of pyridoxine dependency was found in six other enzyme systems studied. In one patient, an abnormally high fasting serum taurine level fell after i.v. pyridoxine administration.

University of Colorado Medical Center
Denver, Colorado

1148 Grenfell, Raymond F., Briggs, Arthur H., & Holland, William C. **Hypotensive effect of some antihypertensive drugs.** Clinical Pharmacology and Therapeutics, 4(2): 162–171, 1963.

The purposes of this part of a 7-year continuing study were: (1) to form a baseline for controlled administration of oral and parenteral placebos that would establish a standard for various antihypertensive agents, and (2) to determine whether or not the lowering of blood pressure with drug or placebo per se would influence complications and survival rate in those with high blood pressure. The effects of placebo, chlorothiazide, hydrochlorothiazide, hydrochlorothiazide plus reserpine, hydrochlorothiazide plus hydrogenated ergot alkaloids, guanethidine, and α-methyldopa given orally to ambulatory outpatients with blood pressure in excess of 150/100 mm Hg are presented. The results for both the sitting and the standing positions are tabulated. Chlorothiazide and hydrochlorothiazide caused a significant decrease in systolic and diastolic blood pressure. Hydrochlorothiazide plus reserpine or the ergot alkaloids caused slightly greater decreases. Guanethidine caused a decrease in systolic and diastolic blood pressure similar to that of oral placebo except in the standing position, where the drug reduced diastolic blood pressure to a significantly greater extent. The α-methyldopa caused a significant decrease in systolic pressure and a more variable reduction in the diastolic. In patients with blood pressure over 200/120 mm Hg, blood pressure decreased significantly after oral placebo. Those with blood pressure under 200/120 mm Hg did not have this effect.

University of Mississippi
Jackson, Mississippi

1149 Gruber, Charles M., Jr. & Baptisti, Arthur, Jr. **Estimating the acceptability of morphine and noracymethadol in postpartum patients.** Clinical Pharmacolgy and Therapeutics, 4(2):172–181, 1963.

This study was made, using postpartum patients, to evaluate favorable and unfavorable responses to two pain-relieving drugs after various doses in order to compare the type of response to the amount used. Groups of 50 patients with uterine cramps were given 15, 30, 60, and 90 mg morphine or 2.5, 5, 10, 20, and 30 mg noracymethadol orally in single doses. Four groups of 50 patients were given blank capsules or 60 mg morphine. Change in pain intensity was directly proportional to and relief of pain was inversely proportional to initial pain. Effectiveness was determined by summing these two estimates of analgesia and was estimated 1, 2, 3, 4, and 6 hours after drug. Noracymethadol was found to be 3.25 times as potent as morphine. Nausea, dizziness, drowsiness, and possibly itching were the only dose-related symptoms after each drug. By relating effectiveness to undesirable effects, noracymethadol produced more analgesia and fewer undesirable effects than did morphine. Eight graphs and two tables are included.

Marion County General Hospital
Indianapolis, Indiana

1150 Wasserman, Albert J. & Richardson, David W. **Human cardiopulmonary effects of doxapram, a respiratory stimulant.** Clinical Pharmacology and Therapeutics, 4(3):321–325, 1963.

Since animal experiments had proved doxapram[1-ethyl-4-(morpholinoethyl)-3,3-diphenyl-2-pyrrolidinone hydrochloride hydrate] to be a potent, centrally acting respiratory stimulant, a study with human beings was made. Thirteen male veterans (45 to 77 years of age) with severe cerebral vascular atherosclerosis (2) and obstructive pulmonary emphysema (11) were given from 23 to 230 mg infused i.v. Dosage depended on the subjects response in regard to augmented respiration, the development of systemic hypertension, or the development of dyspnea. In each patient, minute ventilation increased within a few seconds after infusion. In 12 patients, arterial oxygen tension increased; in 11, arterial carbon dioxide tension decreased. Mean brachial arterial pressure increased in 12 patients. Mean pulmonary arterial pressure rose in two subjects with pulmonary emphysema. Oxygen consumption and cardiac output did not change significantly. There was a greater improvement in oxygen tension than in carbon dioxide tension, suggesting that doxapram not only increases alveolar ventilation but also improves ventilation--perfusion relationships in subjects with emphysema. Doxapram may be useful in the treatment of respiratory depression associated with chronic pulmonary disease.

The systemic and pulmonary pressor effects and the development of dyspnea when larger doses are administered are limiting factors.

Veterans Administration Hospital
Richmond, Virginia

1151 Goldstein, Leonide, Murphree, Henry B., Sugerman, A. Arthur, Pfeiffer, Carl C., & Jenney, Elizabeth H. **Quantitative electroencephalographic analysis of naturally occurring (schizophrenic) and drug-induced psychotic states in human males.** Clinical Pharmacology and Therapeutics, 4(1):10-20, 1963.

This report presents three studies: (1) the characteristics of the quantified EEG from normal subjects without drug and after placebo; (2) measurements from the EEG's of chronic schizophrenics; and (3) the effects of LSD-25 on normal subjects and psychotics. Analysis of the quantified EEG of the left occipital lead of 21 normal male subjects (21 to 30 years of age) revealed an average coefficient of variation in electrical energy of 15.4%. In 25 male chronic schizophrenic patients (23 to 45 years of age), the mean coefficient of variation was 8%. Placebo administration did not produce any significant change in either group. In the normal men, oral dosage with 0.3μg/kg LSD-25 produced a 33% decrease in variability without significant change in the mean energy content of the EEG. When the dose of LSD-25 was increased to 1μg/kg, a 25% decrease in variability and 23% reduction of the energy content of the EEG followed. In schizophrenic patients, LSD-25 at 1μg/kg orally did not affect the mean energy content, but produced a 47% increase in variability. These findings indicate that the EEG of male, institutionalized, chronic schizophrenics tends to be hyperregulated. Similar hyperregulation is produced in normal volunteers by threshold, and larger, doses of LSD-25.

New Jersey Neuropsychiatric Institute
Princeton, New Jersey

1152 Nahas, Gabriel G. **The clinical pharmacology of THAM [tris(hydroxymethyl)-aminomethane].** Clinical Pharmacology and Therapeutics, 4(6):784-803, 1963.

In the beginning of this article, a review of the basic pharmacology of tris(hydroxymethyl)aminomethane (THAM) is given. With respect to clinical pharmacology, THAM is an effective titrating agent because of its buffering capacity, low toxicity, and rapid elimination. The amino alcohol THAM has been used for the correction of acute acidosis during cardiac operation and extracorporeal circulation, cardiac arrest, and massive transfusions with ACD blood. Its use in chronic respiratory acidosis should be restricted to the acute decompensated phase and should be accompanied by mechanical ventilation. Other clinical indications for THAM administration include salicylate and barbiturate intoxication and the metabolic acidosis of diabetes. It is most effective when administered i.v. as a 0.3 M solution in amounts calculated to titrate excess acid in extracellular fluid. The administration of THAM can be given p.o. as a salt in combination with a weak acid, such as citrate. In this form, it is a gastic antacid and will also produce systemic alkalinization. (125 references)

Columbia University
New York, New York

1153 Stránská, T. & Mellan, J. **Účinek Bromadrylu a Phenerganu na duševní činnost. (The effect of Bromadryl and Phenergan on psychic activity.)** Activitas Nervosa Superior, 5:191-192, 1963.

A study was made of the effects of therapeutic doses of the Czechoslovakian drug Bromadryl (meprophenhydramine hydrochloride) on cursory daily activity A group of nine medical students was given 50 mg meprophenhydramine the first day, 56 mg promethazine the second day, and placebo the third day. A control group was given placebo on all three days. Tests of the correctness of motor reactions and of reaction time in discrimination of color stimuli showed that neither drug produced significant change. In another experiment, the continuity of psychic functioning---scanning columns of numbers---was not suppressed by either drug. Finally, a questionnaire showed subjective effects with meprophenhydramine (M), promethazine (Pr), and placebo (P) in the following numbers of subjects: influence on cursory activity---M 2, Pr 7, and P 0; sedative effect---M 4, Pr 8, and P 1; and hypnotic effect---M 3, Pr 7, and P 1. Cold, tremor of lower extremities, and increased perspiration were observed in two subjects on meprophenhydramine, in five subjects on promethazine, and in one subject on placebo. In the present study, meprophenhydramine had no effect on reaction time in comparison to the control group.

Psychiatric Clinic, KU
Hradec Králové, Czechoslovakia

1154 Plzák, M., Fischer, R., Lederová, E., & Tomanová, M. **Metylénová modř v léčbě jedné ze symptomatických forem deprese. (Treatment with methylene blue of one of symptomatic forms of depression.)** Activitas Nervosa Superior, 5:180–181, 1963.

Methylene blue was given to 15 patients who suffered from symptomatic form of depression that developed on a background of arteriosclerosis who resisted all other therapy. The eight hospitalized and seven ambulatory patients included eight males and seven females, 50 to 71 years old, with average age of 58.3. Dosage was 3 or 4 tablets of methylene blue (0.05 g) t.i.d. The condition of the hospitalized patients was evaluated according to a rating scale at least weekly, and ambulatory patients were rated during their visits to the antidepression clinic. Improvement was indicated by the Hajkovy questionnaire test for matched pairs. The study covered five weeks. The uniform test demonstrated improvement in the clinical condition of hospitalized patients after two weeks of therapy. Of the 15 patients, there was marked improvement in 4 patients and partial improvement in 9 patients. The entire group was influenced by the treatment. In the first week of treatment, a condition was obtained similar to the turbulent phase in ataractic treatment. This stage stabilized in the third to fifth weeks or sooner. Side effects of isuria and strangury were observed in almost all patients with methylene blue doses above 0.3 g/day. This was suppressed by a uretic antiseptic. Improvement of headache in some patients confirmed earlier observations of analgesic effect. The present experience of the author indicates that methylene blue may be an effective drug for this symptomatic form of depression.

Ke Karlovu 11
Prague 2, Czechoslovakia

1155 Káclová, J., Nesnídalová, R., & Splíchalová, I. **Potencovaná premedikace ataraktiky ve stomatologii. (Increased premedication with ataractics in stomatology.)** Activitas Nervosa Superior, 5:224–225, 1963.

In a double-blind clinical experiment, drug combinations of meprobamate and chlorpromazine, or meprobamate and benactyzine, or placebo, potentiated in 3 doses, were administered to anxious adults before stomatological surgery. Anxious and rebellious children, 4 to 16 years old, were given combinations of meprobamate and dichlorpromazine, meprobamate and benactyzine, or placebo before cursory stomatological treatment. In the adults, the drugs produced dryness of mucous membranes, drowsiness, overall calmness, loss of anxiety, and euphoria. With placebo, significant emotional manifestation of anxiety, an increased urge to urinate, and an increased pulse rate were observed. In children, the ataractics produced significant drowsiness and loss of motor unrest. Euphoria and polylalia were not statistically significant. Pulse rate increased with all drugs and with placebo also. In asthenic, encephalopathic, or somatically affected children, the ataractics had sedative effect, eliminating the need for more stringent psychotherapy. In view of the data obtained, potentiated premedication was verified. The combination of meprobamate and benactyzine is recommended for ambulatory patients. Motor unrest in children was influenced to a greater extent by the combination of meprobamate and dichlorpromazine.

Psychiatric Division of KÚNZ
Prague, Czechoslovakia

1156 Ingrová, L., Bojanovský, J., & Chloupková, K. **Léčba endogenních depresí přerušovanými dávkami reserpinu. (Treatment of endogenous depression with intermittent doses of reserpine.)** Activitas Nervosa Superior, 5:183–184, 1963.

A group os 24 female patients, 20 to 72 years old, was treated with intermittent doses of reserpine. The diagnoses were: paranoid schizophrenia with depression (1), diencephalic syndrome (1), endroreactive depression (2), atypical melancholy (4), cyclophrenic depression (10), and involutional depression (6). The main syndromes included anxious depressive (7), depressive paranoid (5), anhedonistic (5), and melancholic syndromes (2), plus periodic stupor with anxiety (3). Over a 30-day period, reserpine was given i.p. (3 to 5 mg) to 20 patients, and 4 patients were given 6 mg p.o. every three days, for a total of 10 doses. Clinical rating of the patients showed that of 22 primary depressives, favorable therapeutic results were obtained in 13 patients (59%), 7 patients improved, and 2 patients were unchanged. Best results were obtained with the paranoic-depressive and periodic-stupor forms. Of individual symptoms, the best improvement was obtained in mood, which improvement persisted from the first injection to the end of treatment. Acute anxiety was controlled quickly, and sleep improved up to the end of treatment. Flush syndrome appeared as a side effect with the first injection. In addition, 9 patients reported internal tension, physical unrest, buring sensation in the body, and a feeling of stupor. Digestive disturbances were noted in

three patients, and central hypotension without tendency toward orthostatism in five patients. No favorable results were obtained with schizophrenia and diencephalopathy, although depression changed to euphoria and hebephrenia. The data indicate that reserpine has an effect similar to that of the majority of antidepressive substances.

Psychiatric Clinic, UJEvP
Brno, Czechoslovakia

1157 McCollister, Robert J., Flink, Edmund B., & Lewis, Mary D. **Urinary excretion of magnesium in man following the ingestion of ethanol.** American Journal of Clinical Nutrition, 12:415-420, 1963.

The response of urinary magnesium to ethanol ingestion was studied in three experiments using 12 normal subjects. The amount and type of ethanol ingested, the frequency and time span of urine-specimen collections, and the nutritional state of the subjects, whether fasting or not, were slightly different in each experiment. After alcohol ingestion under varying conditions, the urinary excretion of magnesium increased strikingly in 6 of the 12 subjects. In four of the remaining six, a less striking but definite increase also occurred. It is concluded that magnesium excretion induced by alcohol ingestion, as well as poor dietary intake, probably contributes to magnesium deficiency in chronic alcoholism. (Serum magnesium levels were found to be normal before and after alcohol.)

Veterans Administration Hospital
Minneapolis, Minnesota

1158 Corday, Eliot, Rothenberg, Sanford F., & Irving, David W. **Cerebral angiospasm. A cause of the cerebral stroke.** American Journal of Cardiology, 11:66-71, 1963.

Arteries at the base of the brain of 20 Rhesus monkeys were studied by new photographic techniques to determine if they are capable of vasoconstriction. A window was made in the skull by removing the temporal, parietal, and part of the occipital bones. The temporal lobe of the brain was retracted to photograph the arteries around the circle of Willis. The camera was triggered to a specific phase of the systole by a photoelectric cell focused on the ECG tracing. Stimulation of the intracranial portion of the internal carotid artery by electrical and mechanical means caused vasoconstriction sufficient to induce cerebral ischemia. Administration of epinephrine i.v. caused cerebral vasoconstriction in 7 of 11 experiments. Norepinephrine caused the artery to increase in size in 6 of 11 experiments. Angiospasm continued when the animal breathed carbon dioxide. Papaverine and novocaine often relaxed the vasospasm. Surgical ablation or novocainization of the stellate ganglia did not release the cerebral angiospasm. In conclusion, cerebral angiospasm of the large vessels at the base of the brain can be induced by a traumatic stimulus or i.v. injection of epinephrine. Interruption of the stellate ganglion does not relieve this angiospasm.

Cedars of Lebanon Hospital
Los Angeles, California

1159 Madan, Baldev R. & Pendse, Vinayak K. **Antiarrhythmic activity of thioridazine hydrochloride (Mellaril).** American Journal of Cardiology, 11:78-80, 1963.

Thioridazine hydrochloride was investigated in 10 mongrel dogs of both sexes (15 to 18 kg in weight) for its quinidine-like activity in experimental cardiac arrhythmias simulating clinical disorders. Atrial fibrillation was produced in anesthetized dogs by the topical application of 5% acetylcholine. A self-perpetuating auricular flutter was produced by the method of Rosenblueth and Garcia Ramos. A dose of 1 mg/kg/minute of the drug was injected i.v. until reversion to normal sinus rhythm occurred. For ventricular arrhythmia, the technique of two-stage ligation of the anterior descending branch of the left coronary artery was used. The dogs were studied in the unanesthetized state, 18 to 24 hours after the operation, when their ECT's indicated complete dissociation of atrial and ventricular actively. The drug, diluted in 20 ml of 5% glucose in normal saline, was given i.v. for 5 minutes. Thioridazine caused significant reduction in the duration of acetylcholine-induced auricular fibrillation and brought about reversion of auricular flutter to normal sinus rhythm. It exerted a long-lasting suppressor action on ventricular ectopic tachycardia. These findings, coupled with the low toxicity of the drug, are suggestive of the therapeutic usefulness of thioridazine in selected cases of cardiac arrhythmias.

Medical College of Bikaner
Rajasthan, India

1160 Cole, Seymour L., Kaye, Harry, & Griffith, George C. **Assay on antianginal agents. A long-acting nitrate, psychic energizers and a tranquilizer.** American Journal of Cardiology, 11:639-645, 1963.

The purpose of this study was to determine the effects of seven drugs as antianginal

agents in the prophylactic treatment of 26 patients with angina pectoris (14 men, 47 to 80 years old and 12 women, 49 to 72 years old). A double-blind procedure with multiple control periods was used. Erythrol tetranitrate (60 to 120 mg/day for 3 to 6 weeks) decreased the frequency of anginal attacks and nitroglycerin intake in three of nine patients, but there was never complete remission of attacks. Headache occurred in two patients, but it was not severe enough to stop treatment. When the daily dosage of the four amine oxidase inhibitors used was individualized and the duration of therapy was varied until the optimal dose was achieved, isocarboxazid (10 to 60 mg/day for 2 to 10 weeks) eliminated anginal attacks and nitroglycerin intake in two patients on repeated occasions, and the drug produced good results in 6 more of 12 patients. Phenylisopropylhydrazine (3 to 16 mg/day for 2 to 7 weeks) was effective in 12 of 22 patients, phenelzine (15 to 60 mg/day for 3 to 6 weeks) in 5 of 15, and nialamide (75 to 300 mg/day for 3 to 6 weeks) in 10 of 19 patients. Toxic effects with these four inhibitors were infrequent and were soon controlled by adjusting dosage. Imipramine (75 to 150 mg/day for 3 to 6 weeks) decreased the frequency of anginal attacks and nitroglycerin dosage in 3 of 12 patients, an effect not consistently repeatable. Mild hypotension and nausea were uncommon side effects. Chlordiazepoxide (10 to 30 mg/day for 2 to 4 weeks) reduced general anxiety in 5 of 15 patients and decreased the frequency of anginal attacks and nitroglycerin intake in 3. Drowsiness and depression in five patients caused reduction in dosage.

University of California School of Medicine
Los Angeles, California

1161 Torosdag, Seta, Schvartz, Natalio, Fletcher, Lucian, Jr., Fertig, Harrison, Schwartz, M. Stephen, Quan, Richard B. F., & Bryant, J. Marion. **Pargyline hydrochloride as an antihypertensive agent with and without a thiazide.** American Journal of Cardiology, 12:822-827, 1963.

This is a report of the antihypertensive and side effects of pargyline hydrochloride in 64 ambulatory hypertensive patients who were observed for 16 months. In 10 of these patients, the effects of pargyline alone are compared to those of pargyline plus a thiazide diuretic, methyclothiazide. Pargyline was given alone starting with 25 mg/day. Increments of 25 mg were added to the daily dose at intervals of 2 or more weeks until a satisfactory hypotensive response or undesirable side effects appeared. In 10 patients, after an interim placebo period of 2 or more weeks, pargyline was administered concomitantly with methyclothiazide (5 mg/day for 2 weeks, thereafter dosage was 10 mg/day). After 3 to 7 weeks of methyclothiazide, pargyline was added to this regimen. The mean blood-pressure changes are tabulated. Pargyline was found to be a potent antihypertensive agent and, when used as an adjunct to sulfonamide diuretics, is of value in the treatment of essential hypertension. Side effects were typical of MAO inhibitors. Insomnia, dizziness, weakness, nervousness, and weight gain were most frequent, but these were mild and receded when dosage was reduced. The lack of correlation between the antihypertensive effects and side effects of pargyline raises doubt as to a causal relationship between MAO inhibitory and hypotensive actions of this type of drug.

New York University Post-Graduate Medical School
New York, New York

1162 Lillehei, Richard C., Longerbeam, Jerrold K., & Bloch, Jack H. **Physiology and therapy of bacteremic shock. Experimental and clinical observations.** American Journal of Cardiology, 12:599-613, 1963.

Studies of the nature of the hemodynamic effects of endotoxin, of methods to alter such effects, and of the clinical application of such studies are summarized. Dogs were used in all studies. The sympathomimetic action of endotoxin and its ability to increase the output of catecholamines seem to be the principal means by which endotoxin induces its pernicious effects. With the resultant limitation in blood flow, ischemic and stagnant visceral anoxia occur. Phenoxybenzamine, which has a direct adrenergic blocking effect, and hydrocortisone, which indirectly blocks sympathomimetic actions, prevent these deleterious consequences of endotoxin and spare visceral organs. Vasopressor drugs commonly used to treat patients with bacterial shock either have no effect or they increase visceral ischemia. An effective therapeutic regimen is described for human beings.

University of Minnesota Medical School
Minneapolis, Minnesota

1163 Somers, John E., Irwin, Richard L., & Shy, G. Milton. **The use of lycoramine derivatives in myasthenia gravis.** Neurology, 13(11):543-553, 1963.

In this study, patients (12 to 65 years old) with myasthenia or myasthenia gravis were given both types of lycoramine---the i.v. short-

acting deoxydemethyllycoramine methiodide (all eight subjects) or the oral longer-acting deoxydemethyldimethylcarbamate lycoramine hydrochloride (three of the eight subjects). Effective doses for the i.v. form ranged from 0.005 to 0.1 mg/kg, and those for the oral form ranged from 0.1 to 0.5 mg/kg. Both forms had definite nicotinic and muscarinic effects compatible with anticholinesterase activity. The observations suggest a preferential effect on the ocular and bulbar muscles. The oral form has been used successfully with or without other anticholinesterases for up to 17 days. The usual side effects of anticholinesterases were seen in the higher doses, including the danger of significant overdose (0.2 mg/kg produced transient unconsciousness in a 29-year-old woman). The potential usefulness of the oral form in treatment and the i.v. form in diagnosis warrants further investigation.

National Institutes of Health
Bethesda, Maryland

1164 Rasmussen, Theodore & Gossman, Henry. **Epilepsy due to gross destructive brain lesions. Results of surgical therapy.** Neurology, 13:659-669, 1963.

Followup data, covering periods from 1 to 24 years (median period, 6 years), are presented for 85 patients who were operated on for seizures caused by, or associated with, large destructive lesions involving more than one lobe of the brain. The patients were all refractory to anticonvulsant drugs. Brain damage resulted from birth injuries, inflammatory brain injuries, postnatal head injuries, or gunshot wounds. Four types of operation were performed: total hemispherectomy, subtotal hemispherectomy, local excision, and staged removals. Case histories are given for each type of operation. Thirty-one patients had no further seizures after leaving the hospital, and another eight patients became seizure free after a few early postoperative seizures. In 24 patients, seizure frequency was markedly reduced; in 22 patients, results were considered unsatisfactory.

McGill University
Montreal, Canada

1165 Coons, W. H., Boyd, B. A., & White, J. G. **Chlorpromazine, trifluoperazine and placebo with long-term mental hospital.** Canadian Psychiatric Association Journal, 7:159-163, 1963.

A group of 117 female long-term mental-hospital patients (mean age, 47.5 years), judged to be suitable for tranquilizing medication, were randomly assigned to three treatment groups: one received chlorpromazine (50-mg capsules), one received trifluoperazine (5-mg capsules), and one received placebo. Dosage prescribed was three capsules per day. The trial lasted 6 weeks. Assessment of adjustment to the hospital by the Hospital Adjustment Scale revealed no significant group differences in response to treatment after either 3 or 6 weeks. Comparison of each group's level of adjustment at the beginning, middle, and end showed a similar absence of significant differences. Inspection of the scores of individuals in each group, however, indicated that there was wide variability in the interindividual responses to all three treatment conditions. The implications of these findings for the management of long-term patients and for further study are discussed.

Dalhousie University
Halifax, Nova Scotia

1166 Lamphier, Timothy A. **Evaluation of chlormezanone as a clinical and postoperative central relaxant and tranquilizer.** Clinical Medicine, 69:109-111, 1962.

A series of 83 ambulatory patients (62 males and 21 females, aged 13 to 72 years) with various complaints related to the musculoskeletal system were treated with 100 or 200 mg chlormezanone three or four times daily. Response to therapy was excellent in 66%, good in 20%, fair in 10%, and poor in 4%. There were 11 instances of side effects. These included dizziness, nausea, weakness, rash, and flushing; the drug was discontinued in one patient. It is concluded that chlormezanone is a safe and effective agent in the treatment of a variety of musculoskeletal conditions.

Boston, Massachusetts

1167 Hollister, Leo E. & Hartman, Alan M. **Mescaline, lysergic acid diethylamide and psilocybin: Comparison of clinical syndromes, effects on color perception and biochemical measures.** Comprehensive Psychiatry, 3(4):235-241, 1962.

Mescaline (5 mg/kg), LSD-25 (1μg/kg), and psilocybin (150μg/kg) were studied in 20 screened subjects, with 18 receiving all three drugs. Drugs were administered orally under similar test conditions; doses were fixed; assignments to drug followed a latin-square sequence; and the subjects were unaware of the identity of each drug. Clinical syndromes were assessed by a questionnaire after each trial. Color perception was

studied by both adequate and inadequate stimuli for eliciting color phenomena, and measurements were taken before and 2 hours after drug administration. Selected biochemical and physiologic measurements were also made. Clinical syndromes were found to be comparable in kind and degree in all three drugs, that from mescaline being most pronounced. Somatic manifestations predominated; psychotomimetic symptoms were not common. Color perception was not altered much when adequate stimuli were used, but it was enhanced with inadequate stimuli. Only minor differences in color perception were noted among the three drugs. All the drugs significantly decreased urinary excretion of inorganic phosphorus, increased plasma-free fatty acids, and decreased total circulating eosinophils. The only other significant change was an increase in copper oxidase activity after psilocybin. Because of their similarities, it might be assumed that the three drugs have many common mechanisms of action despite their chemical differences.

Veterans Administration Hospital
Palo Alto, California

1168 Azima, H., Silver, A., & Arthurs, D. **The effects of G-33040 in depressive states: A multi-blind study.** American Journal of Psychiatry, 119:465–466, 1962.

This article reports on a controlled study of G-33040, 4-[3-(5H-dibenz[b,f]azepin-5-yl)propyl]-1-piperazine ethanol dihydrochloride, administered multiblind to three groups of depressed patients, each group containing 20 neurotics and 10 psychotic depressives. One group (9 males and 21 females; average age, 45 years) received an average daily dose of 100 mg of drug for an average period of 25 days; the other two groups (13 males and 17 females in each; average age, 40 years) received a potent placebo (phenobarbital, 50 mg/day) and an inert placebo, respectively, for an average of 21 days each. The tests showed that G-33040 is an adequately potent antidepressant, which reaches statistical significance beyond the 0.05 level. The drug seems to be especially effective in neurotic depressive states, and the relative lack of side effects and sedative properties adds to its suitability for ambulatory patients.

McGill University
Montreal, Canada

1169 Vencovský, E., Peterová, E., Šedivec, V., & Baudiš, P. **Předběžné klinické zkušenosti se Surmontilem. (Preliminary clinical experiences with Surmontil.)** Activitas Nervosa Superior, 5:178, 1963.

Surmontil (trimepropimine), a compound with an imipramine core and a ramified aliphatic levomepromazine chain, was given to 26 patients (including 16 females), 19 to 70 years old, who had the following diagnoses: endogenous depression (8); involutional depression (6); neurotic depression (4); psychotic syndrome, including melancholy (6); and depressive schizophrenia (2). Dosage ranged from 150 to 450 mg/day (mean: 250 mg/day). During the first few days, the drug was administered parenterally. Symptomology was rated according to the FKD (Hamilton—Bujanovsky) scale. Results showed marked improvement in 4 cases (decrease in score of at least 80%); little improvement in 3 cases (drop of 40% to 60% of original score); no improvement in 13 cases (less than 40% drop in score, worsening, and relapse). Depressive neurotics predominated in the group showing marked improvement, whereas the group showing no improvement consisted of patients with psychotic depression and nonpsychotic endogenous depression. Side effects were insignificant, and were similar to those of imipramine. The drug had a slight synchronizing effect on the EEG. According to preliminary experience with trimepropimine, it has low toxicity and favorable action on depression, anxiety, and apathy (mainly of neurotic origin), but it is considerably less effective than imipramine and levomepromazine.

Psychiatric Clinic, KU
Plzeň, Czechoslovakia

1170 St. Laurent, J., Cahn, C. H., & Ban, T. A. **Treatment of psychiatric patients with a phenothiazine derivative (prochlorperazine) with special reference to after care.** American Journal of Psychiatry, 118(10):938–940, 1962.

A report is made of the effects of prochlorperazine used in mental hospitals and in aftercare situations. A group of 152 patients (56 males and 96 females, 18 to 74 years of age) of various diagnoses were surveyed. While in the hospital, 45 patients had to discontinue using prochlorperazine, but 91 changed from other drugs to prochlorperazine. In the aftercare clinic, 93 of the above patients were observed. Of these, 69 were

schizophrenics or paranoids; 44 (63%) of these psychotics improved and 25 (37%) did not. In conclusion, prochlorperazine is an effective drug for acute psychotic conditions, especially schizophrenia and paranoia. Frequent side effects (in 80 of 152 patients, or 53%), especially extrapyramidal, were controlled by the addition of antiparkinsonian drugs.

Verdun Protestant Hospital
Verdun, Quebec, Canada

1171 Brooks, Clyde. **The new role of the general practitioner in the treatment of mental cases with the new psychobolic drugs. A report on the benefits derived from the use of reserpine in mental patients.** Louisiana State Medical Society, 114:292-293, 1962.

In this review, the author proposes calling some of the new tranquilizers, psychobolics ("mind changers"), since that is their effect on patients. It is stated that with these new drugs and through the general physician's help, the population in mental hospitals can be reduced. An example of these drugs is reserpine---it is safe and effective and can be used by the general physician. The side effects of reserpine are discussed, in addition to the three main ways to treat mental cases---psychotherapy, shock therapy, and medical therapy. Even the worse cases can be helped by this treatment.

The Alabama State Hospitals
Tuscaloosa, Alabama

1172 Iasky, Julian J., Klett, C. James, Caffey, Eugene M., Jr., Bennett, J. Lamar, Rosenblum, Marcus P., & Hollister, Leo E. **Drug treatment of schizophrenic patients. A comparative evaluation of chlorpromazine, chlorprothixene, fluphenazine, reserpine, thioridazine and trifluprom azine.** Diseases of the Nervous System, 23:698-706, 1962.

A double-blind study of the relative clinical effectiveness of chlorpromazine, chlorprothixene, fluphenazine, reserpine, thioridazine, and trifluprom azine was conducted with 512 male schizophrenics for 24 weeks. Dosage was gradually increased in a predetermined manner for the first 4 weeks and was then individualized for the remaining 20 weeks within the following daily limits: chlorpromazine and thioridazine, 200 to 1,600 mg; chlorprothixene and trifluprom azine, 50 to 400 mg; fluphenazine, 2.5 to 20 mg; and reserpine, 1.5 to 12 mg. Analyses of behavior-rating-scale data revealed a variety of differences among drugs, particularly in syndromes associated with excitement—retardation. A multivariate analysis yielded the following rank order of effectiveness: chlorpromazine, thioridazine, fluphenazine, chlorprothixene, trifluprom azine, and reserpine. Only the differences between reserpine and the three most effective drugs were significant. Complications of any kind were not a major problem during the study, and those side reactions that did occur were, for the most part, equally distributed among the treatment groups.

Veterans Administration Central NP
Research Laboratory
Perry Point, Maryland

1173 Green, Joseph B. **The activation of electroencephalographic abnormalities by tolbutamide-induced hypoglycemia.** Neurology, 13(1):192-200, 1963.

Based on experimental evidence that hypoglycemia can disclose cerebral lesions that produce few overt signs, a hypoglycemic state was induced by tolbutamide in patients suspected of having cerebral disease. Sixty patients, with diagnoses ranging from "anxiety state" to cerebral tumor, were studied. A 30- to 40-minute control electroencephalogram was run on each patient before the induction of hypoglycemia. True blood sugar (Somogyi method) was determined before injection of tolbutamide and at varying intervals afterward. Thirty-three patients from all diagnostic categories had normal control EEG's. Of these, 17 exhibited diagnostic EEG abnormalities after tolbutamide. Tolbutamide-induced hypoglycemia revealed abnormalities, whether the patient's attacks were grand mal, psychomotor, or "syncopal." The incidence of EEG abnormalities failed to correlate with the degree or rapidity of drop in blood-sugar level, the presence of hypoglycemic symptoms, or the age of the patient. Nine case histories, illustrating various diagnostic categories and EEG responses, are presented.

Pennsylvania Hospital
Philadelphia, Pennsylvania

1174 Kantarjian, Artin D. & Shasheen, Abdul Sattar. **Methyl bromide poisoning with nervous system manifestations resembling polyneuropathy.** Neurology, 13: 1054-1058, 1963.

A study is presented of eight cases of accidental methyl bromide poisoning. The patients, all men, 19 to 43 years of age, were known to have been exposed to low concentrations of methyl bromide vapor for 6 to 8 hours daily, 6 days a week, for about 3 months. Clinical manifestations were neurologic, akin to peripheral neuropathy. Paresthesias were the earliest manifestations, followed by sensory deficits and weakness in the distal portions of the extremities. The lower extremities were involved to a greater extent than the upper ones. Marked unsteadiness of gait was noted in six patients. The deep reflexes were either absent or sluggish. No patient in this group experienced severe systemic ill effects of methyl bromide intoxication. Recovery was spontaneous and complete 6 to 8 months from the onset of the illness.

University of Baghdad College of Medicine
Baghdad, Iraq

1175 Krakowski, A. J. **Efficency and safety of i.v. nialamide in treatment of depressive syndromes.** Diseases of the Nervous System, 24(7):434-439, 1963.

In this study, 47 patients (40 women, 27 to 70 years of age; 7 men, 24 to 66 years of age) with severe neurotic and endogenous depressions received from one to seven 750-mg doses daily of nialamide i.v., followed by maintenace therapy of 75-mg doses daily of nialamide orally. In most cases, i.v. nialamide was given on alternate days, and 75 mg of oral nialamide was given on the intervening days. One to 10 months after the i.v. therapy, the recovery rate of 75% greatly exceeded the usual spontaneous remission. Both neurotic and endogenous depression showed a remission rate exceeding the improvement rate observed with oral nialamide. Side reactions were mild and did not require discontinuance of the drug. Nialamide, in this series, proved nontoxic to the liver, kidneys, and the hemopoietic organs. The data obtained are tabulated.

Champlain Valley and Physicians Hospitals
Plattsburgh, New York

1176 Itil, T., Stoeger, R., & Rajotte, P. **Clinical and electroencephalographic study of a new hypno-sedative combination and its constituents.** Diseases of the Nervous System, 24(8):476-483, 1963.

Clinical and EEG studies were made with a hypnotic--sedative agent containing 20 mg prothipendyl and 100 mg cyclobarbital calcium in a tablet, and 40 mg prothipendyl and 150 mg cyclobarbital in an ampule. Trials were conducted with patients who suffered from light functional sleep disturbances, severe insomnia, and psychomotor agitation. The depth and duration of sleep induced by the combination and by each component administered i.v. separately, in varying doses, were measured with the EEG. The changes produced on the characteristic EEG thiopental pattern by prior administration of the combination and of each component were also examined. The combination was given to 200 patients with sleep disturbances, and its effects were compared to those of barbiturates, nonbarbiturate hypnotics, and tranquilizers. The combination induced deeper and longer sleep than each of its components given separately in doubled amounts. The mechanisms of action of both the components and the combined agents are discussed.

Missouri Institute of Psychiatry
St. Louis, Missouri

1177 Piuck, Charlotte Levin. **Clinical impressions of hydroxyzine and other tranquilizers in a child guidance clinic.** Diseases of the Nervous System, 24(8):483-488, 1963.

In order to determine which psychopharmacologic drugs could effectively, quickly, and safely control prominent symptoms of emotional disturbance in children, eight tranquilizers---hydroxyzine, chlorpromazine, thioridazine, perphenazine, trifluoperazine, chlordiazepoxide, deanol, and meprobamate--- were tested. Twenty-three boys and three girls, 4-$\frac{1}{2}$ to 14-$\frac{1}{2}$ years of age, with diagnoses of mild brain damage (11 patients), adjustment reaction of childhood (14 patients), and mental deficiency (1 patient) were used in the study. The patients acted as their own controls, and major interest was focused on the effects of hydroxyzine. Dosage of hydroxyzine was initiated at 10 mg t.i.d., and other drugs were given as prescribed in the literature. Hydroxyzine proved effective in 10 patients, partially effective in 5, and ineffective in 11. Of

those patients with fair or poor response to hydroxyzine, 15 were tried on other drugs. Three case histories are given to illustrate treatment response. Side effects of hydroxyzine were mild gastrointestinal upset, drowsiness, and temporary overstimulation.

649 East 22nd Street
Brooklyn, New York

1178 Vaisberg, Maurice & Saunders, John C. **Treatment of dyskinesias including Huntington's chorea with thiopropazate and R-1625.** Diseases of the Nervous System, 24(8):499-500, 1963.

This study was conducted in order to make a further determination of the known value of thiopropazate and of the, as yet unknown, efficacy of R-1625, 1-(3-p-fluorobenzoylpropyl)-4-p-chlorophenyl-4-hydroxypiperidine), in the treatment of dyskinesias and hyperkinetic phenomena in Huntington's chorea and other neurological syndromes. Nine patients, three males and six females (40 to 65 years of age), were given either thiopropazate (10 to 20 mg t.i.d.) or R-1625 (1 to 2 mg/day); six of these patients had Huntington's chorea. With thiopropazate, two patients with Huntington's chorea received 60% and 90% relief; one was benefited for only 2 months; two were not helped; and one cerebellar ataxia case and one gas-poisoning (behavior problem) case improved in 10 days; one patient with Huntington's chorea showed 50% improvement, but one patient became worse. The use of these agents at this stage is concluded to be empirical, and further study is needed in their application to hyperkinetic dyskinesias.

Rockland State Hospital
Orangeburg, New York

1179 Winfield, Don L. **The use of diazepam in clinical electroencephalography.** Diseases of the Nervous System, 24(9):524-547, 1963.

Diazepam was used for sedative purposes in a series of 316 psychiatric referrals (3 to 71 years of age) for EEG's. Diagnostic categories included schizophrenics, epileptics and epileptic equivalents, alcohol or drug addicts, organic brain damage, and reactive depression, as well as psychotics and psychoneurotics. (These patients are often difficult to sedate, and, in EEG recording, there is also the problem of the inhibition of muscular activity capable of introducing artifacts into the record and obscuring the brain waves.) The patient was sedated upon arrival, and in 15 to 20 minutes, the electrodes were applied and recording was started. If, after 30 minutes, the patient did not appear to be relaxed, he was given a repeat dose. In the first 34 patients, doses ranged from 5 to 20 mg (according to age), but as a result of further information from the manufacturer, the dosage range was increased from 10 to 25 mg. Repeat doses were usually smaller. An excellent state of drowsiness was obtained in 114 patients, and a good state was obtained in 118; i.e., 73.4% of the patients had satisfactory results. In 55 patients, drowsiness was fair, and in 29, it was poor. Only 31 patients failed to fall asleep. One EEG was technically unsatisfactory. Side effects were negligible and, despite possible underdosage, the new agent was considered superior to previous sedatives in gaining patient cooperation and in obtaining clear records. Also, since the population included 111 behavior-problem children and youths who were extremely resistant to sedation, the results are considered excellent.

University of Tennessee
Memphis, Tennessee

1180 Winnik, H. Z., Assael, M., & Tomin, B. **Therapeutic effects of thioridazine.** Diseases of the Nervous System, 24(9):552-558, 1963.

A therapeutic appraisal of 50 patients treated with thioridazine is presented. The patients, 11 men and 39 women, 15 to 80 years of age, were selected according to target signs (psychomotor restlessness, tension, and anxiety) and to refractoriness to previous treatments and untoward side effects necessitating discontinuation of previous drug therapy. Initial doses of 300 to 500 mg thioridazine daily were given. If no response was observed by the third or fourth week, dosage was increased 100 mg. Improvement was seen in 82% of the patients. Most successfully controlled were tension, anxiety, and psychomotor restlessness. Side effects were mild, with galactorrhea seen in 8 patients, dry mouth in 2, orthostatic hypotension in 1, and vertigo in 1. Thirty patients were given, in addition, the following laboratory tests before treatment and

before reduction of maximum dosage: Funkenstein Test, capillary blood pressure, total blood protein, albumin/globulin ration, cholesterol blood level, and basal metabolism rate. These tests are assumed to be indicators of autonomic-system function. The laboratory changes were paralleled by improvements in the clinical picture of the patients.

Hebrew University Medical School
Jerusalem, Israel

1181 Love, Julian. **Diazepam in treatment of emotional disorders.** Diseases of the Nervous System, 24(11):674-677, 1963.

Diazepam was given to 74 patients (46 females and 28 males, 22 to 83 years of age) with various emotional disorders---14 had anxiety neurosis, 32 had situational neurosis, and 28 had miscellaneous somatic disorders with emotional symptoms. The two predominant complaints were insomnia and nervousness. The drug was given in doses ranging from 1 to 10 mg b.i.d. or t.i.d. Eleven patients also received additional drug therapy. The treatment lasted from 2 days to 3-$\frac{1}{2}$ months. Marked improvement (total or marked remission of symptoms) was noted in 60.8% of the patients, moderate improvement (partial remission) in 27%, and minimal improvement (slight or no remission) in 12.2%. Side effects occurred in 12 patients; these consisted of drowsiness (nine patients), and drowsiness with unsteadiness and shakiness, maculopapular rash, and exfoliative dermatitis (one patient each). Five patients had to discontinue the drug because of the side effects. These results suggest the future usefulness of diazepam in emotional disorders. The drug is particularly effective as a hypnotic when insomnia, in addition to emotional symptoms, is present. No evidence of antiphobic effects in alcoholics was noted.

The Arcadia Clinic
1108 South Baldwin Avenue
Arcadia, California

1182 Lorr, Maurice, McNair, Douglas M., & Weinstein, George J. **Early effects of chlordiazepoxide (Librium) used with psychotherapy.** Journal of Psychiatric Research, 1:257-270, 1962.

A 4-week, double-blind study was made of the early effects of chlordiazepoxide on a group of 150 male outpatients accepted for individual psychotherapy. The hypotheses tested were that there would be a greater reduction in anxiety and tension: (1) in groups receiving psychotherapy than in those without psychotherapy; (2) in groups receiving chlordiazepoxide than in those receiving placebo; and (3) in groups receiving some medication than in groups receiving no medication. Results were based on patient and therapist ratings. According to patient ratings, placebo and the drug were equally effective; patients receiving capsules (either drug or placebo) showed greater overall improvement than those not receiving capsules; and patients receiving capsules plus psychotherapy showed no greater improvement than capsules alone. According to therapists ratings, patients receiving psychotherapy and the drug showed more improvement than those on placebo; and patients receiving either drug or placeo showed more improvement than those on psychotherapy alone.

Veterans Administration, Outpatient Psychiatric Research Laboratory
Washington, D.C.

1183 Klerman, Gerald L., Schildkraut, Joseph J., Hasenbush, L. Lee, Greenblatt, Milton, & Friend, Dale G. **Clinical experience with dihydroxyphenylalanine (DOPA) in depression.** Journal of Psychiatric Research, 1:289-297, 1963.

A clinical trial of DOPA was undertaken as an indirect test of the catecholamine theory of depression. Previous studies have shown that DOPA is a precursor in the synthesis of catecholamines, crosses the blood--brain barrier in animals, and reverses the behavioral and biochemical effects of reserpine. These effects are enhanced by pretreatment with an MAO inhibitor. Assuming that the reserpinized animals represent a possible analog of some human depressions, DOPA was administered alone and in combination with MAO inhibitor. The patients were female, with a median age of 52. The clinical trial was conducted under two conditions: (1) seven depressed patients were treated with DOPA (600 to 1,000 mg daily) for up to 5 weeks; (2) five patients received a combination of phenelzine (45 to 60 mg daily) and DOPA (40 to 800 mg daily) for periods of from 1 to 5 weeks. There was no evidence of clinical improvement under either condition. Transient hypertensive effects were observed in the patients receiving DOPA and MAO inhibitor. These findings are discussed in the light of possible differences between human and animal subjects and the discrepancies in

dosages employed in this study, compared with those usually administered in animal experiments. The implications of these findings for the theory relating catecholamines to disturbed affective states are discussed.

Massachusetts Mental Health Center
Boston, Massachusetts

See also: 1067, 1069, 1070, 1085, 1086, 1092, 1093, 1094, 1099, 1100, 1101, 1106, 1111, 1113, 1114, 1115, 1117, 1118, 1119, 1121, 1124, 1127, 1128, 1129, 1130, 1131, 1132, 1135, 1136, 1137, 1139, 1140, 1195, 1214, 1233, 1284

SIDE EFFECTS

1184 Fullerton, A. G. & Morton-Jenkins, D. **Methyldopa and depression.** (Letter: comment on letters by J. Mielczarek & U. C. Dubach.) British Medical Journal, 1(5329): 538-539, 1963.

A case of toxic psychosis is reported in a 34-year-old woman under treatment with methyldopa for hypertension following pre-eclamptic toxemia. The patient's blood pressure on admission was 160/120, and she complained of headache and visual disturbance. Treatment was instituted with i.v. infusion of 250 ml of 5% dextrose containing 100 mg chlorpromazine, 100 mg promethazine, and 100 mg pethidine. Following a second similar infusion, her blood pressure fell to 140/100, and she was placed on 250 mg methyldopa t.i.d.; this dose was raised to 500 mg t.i.d. over a 3-day period, and maintained at that level. After 5 days, she had a normal delivery. After 7 g of methyldopa had been given, the patient developed toxic psychosis, resembling the symptoms of schizophrenia. Intravenous parentrovite was given, and the patient made an excellent recovery.

Herrison Hospital
Dorchester, England

1185 Blackwell, B. **Tranylcypromine.** (Letter) Lancet, 2:414, 1963.

In 12 people taking tranylcypromine, pronounced hypertension and headache appeared shortly after eating cheese. The random occurrence of these symptoms on any dosage, and after extremely variable duration of medication, strongly suggests an exogenous factor, particularly since patients have continued the drug without a recurrence of the symptoms.

Maudsley Hospital
London, SE. 5, England

1186 Maan, S. S. **Tranylcypromine and cheese.** (Letter) Lancet, 2(7308): 639, 1963.

A woman of 26 reported occasional headaches for 9 weeks while taking 1 tablet (10 mg) of tranylcypromine b.i.d. Medication was changed to tranylcypromine plus trifluoperazine, 1 tablet b.i.d., and after 4 weeks, she reported disabling severe occipital headaches of increasing intensity. It was discovered that she ate daily large quantities of cheese. The tranylcypromine plus trifluoperazine was discontinued, and the symptoms disappeared after a week.

Middlewood Hospital
Sheffield, England

1187 Tec, Leon. **Unexpected effects in children treated with imipramine.** American Journal of Psychiatry, 120:603, 1963.

Some unexpected effects in enuretic children treated with imipramine hydrochloride are given. Twenty-six children, ranging in age from 5 to 14 years, were given 50 mg daily one hour before bedtime. Good success was accomplished, but in three cases, the following reactions were encountered: (1) A 9-$\frac{1}{2}$ year-old boy with a history of status epilepticus developed an allergic rash on the left forearm when treated with imipramine; the rash subsided with discontinuation of medication. (2) An aggressive boy, age 8-$\frac{1}{2}$, subject to sleepwalking, became more aggressive until the imipramine was discontinued. (3) A 13-year-old boy, who since infancy would bang his head violently, even in his sleep, stopped this behavior completely when treated with imipramine.

Mid-Fairfield Child Guidance Center
Norwalk, Connecticut

1188 Dorrell, William. **Tranylcypromine and intracranial bleeding.** (Letter) Lancet, 2(7304):414, 1963.

Three cases of intracranial bleeding associated with the use of tranylcypromine have been reported. One of the patients had taken methylamphetamine concomitantly, and another had a congenital aneurism of a cerebral artery.

The Middlesex Hospital
London, W.1. England

1189 Huttenlocher, Peter R. **Accidental glutethimide intoxication in children.** New England Journal of Medicine, 269(1):38-39, 1963.

Two cases of accidental intoxication with glutethimide occurred in children (about 6 years old) who ingested 2 to 4 times the therapeutic dose. Following a 500 to 1,000 mg dose, the patient's symptoms included cerebellar ataxia, nystagmus, symmetrically dilated pupils, and fluctuating drowsiness that persisted for about 24 hours. Both patients recovered completely.

Harvard Medical School
Boston, Massachusetts

1190 Long, Michael T., Childress, Richard H., & Bond, William H. **Megaloblastic anemia associated with the use of anticonvulsant drugs. Report of a case and review of the literature.** Neurology, 13: 697-702, 1963.

A case of megaloblastic anemia occurred in a 47-year-old man who was being treated with anticonvulsants. Twenty days after folic acid therapy was initiated (10 mg b.i.d.), bone-marrow examination revealed normoblastic erythropoiesis. After discharge, the patient was continued on folic acid and restarted on anticonvulsants. Data from 78 cases of megaloblastic anemia reported since 1952 are reviewed.

Veterans Administration Hospital
Indianapolis, Indiana

1191 McFarland, Robert B. **Fatal drug reaction associated with prochlorperazine (Compazine). Report of a case characterized by jaundice, thrombocytopenia, and agranulocytosis.** American Journal of Clinical Pathology, 40(3):284-290, 1963.

A 73-year-old woman was admitted to a hospital with upper abdominal pain, weakness, pallor, sweating, left-arm numbness, nausea, and vomiting. Physical examination, laboratory findings, and an EEG were thought to indicate left ventricular hypertrophy. Myocardial infarction and cholelithiasis were also suspected. Coumadin, prochlorperazine, vitamins, chloral hydrate, and milk of magnesia were prescribed. On the 28th hospital day, the patient began to run a low-grade fever and white blood counts started to fall. On the 33rd day, petechiae were noted, and prochlorperazine was discontinued after 31 days of continuous administration. On the same day, her temperature rose and continued to spike twice daily thereafter. Nitrofuran was prescribed for a suspected urinary infection. With the onset of agranulocytosis and thrombocytopenia, the patient's condition deteriorated further, then improved somewhat. By the 40th day, an erythematous rash had developed, and she became lethargic. Her bilirubin rose and the white-cell count fell to 900. The patient died in shock on the 44th hospital day. Postmortem studies revealed septicemia and severe hepatic damage. When the case was reviewed, it was felt that prochlorperazine was the cause of hepatic necrosis.

Denve General Hospital
Denver, Colorado

1192 von Ledebur, I., Frommel, Ed., & Béguin, M. **Nalorphine antagonism to the narcotic action of chlorpromazine, meprobamate and metaminodiazepoxide (Librium).** Medicina Experimentalis, 7:177-179, 1962.

Chlorpromazine (30 mg/kg, s.c.), meprobamate (100 mg/kg, p.o.), or metaminodiazepoxide (5 and 10 mg/kg, p.o.) was administered to groups of guinea pigs. A second group of guinea pigs received the same medication with nalorphine, 10 mg/kg s.c., added. Nalorphine significantly reduced the sleeping time induced by chlorpromazine (47%), meprobamate (82%), and metaminodiazepoxide (66% and 11%).

Geneva University School of Medicine
Geneva, Switzerland

See also: 1067, 1071, 1072, 1073, 1080, 1082, 1083, 1100, 1102, 1107, 1112, 1141, 1142, 1163, 1175, 1179, 1202, 1207, 1238, 1243

1193 Pare, C. M. B. & LaBrosse, Elwood, H. **A further study on alleviation of the psychological effects of LSD in man by pretreatment with 5-hydroxytryptophan.** Journal of Psychiatric Research, 1:271-277, 1962.

To ascertain if a clinically apparent alleviation of LSD-25 symptoms might be obtained by pretreatment with 5HTP, a higher (maximum) dose of 5HTP was used than had been used previously. Nine female and four male subjects (18 to 25 years of age), all in good health, were given a preliminary treatment of 25 to 60 mg dl-5HTP or 0.9% saline solution, followed in 1 hour by 30μg to 60μg LSD-25. The pretreatment was given in a double-blind design; all drugs were given i.v. One week later, the procedure was repeated, with the subjects receiving the alternative pretreatment. The Symptoms Rating Scale was administered before, $\frac{1}{2}$, and 1 hour after the pretreatment, and $\frac{1}{2}$, 1, 2, and 3-$\frac{1}{2}$ hours after LSD-25. The results from this scale showed significantly ($P < 0.02$) fewer symtoms $\frac{1}{2}$ hour after LSD-25 when 5HTP was the pretreatment. Results on the Clyde Mood Scale showed an LSD-25 effect, but no significant effect of pretreatment. Mild gastrointestinal symptoms and, occasionally, a slight fall of blood pressure resulted from 5HTP, but these effects subsided in 20 to 30 minutes. These results strengthen the conclusion that pretreatment with 5HTP decreases the symptoms produced by LSD-25.

St. Bartholomew's Hospital
London, EC.1, England

1194 Penick, S. B. & Hinkle, Lawrence E., Jr. **The effect of glucagon, phenmetrazine and epinephrine on hunger, food intake and plasma nonesterified fatty acids.** American Journal of Clinical Nutrition, 13:110-114, 1963.

The effects of glucagon on nonsterified fatty-acid levels and hunger were compared with those of phenmetrazine and epinephrine. Ninety-four experiments were carried out on four healthy young men. They arrived for the twice-weekly tests after a 4-hour fast. A questionnaire designed to assess their degree of hunger was completed before and during the tests. In one series of experiments, the subjects were given either 1 mg glucagon i.m. or placebo upon arrival and either 25 mg phenmetrazine p.o. or placebo 1 hour later. A test meal was served at 2 hours. In another series of experiments, either 0.2 mg of epinephrine i.m. or placebo was given 30 minutes before a test meal. Blood was drawn on arrival and at 30-minute intervals for determination of plasma nonesterified fatty-acid levels by the method of Dole. Glucagon caused an initial fall in the levels and then a rise; epinephrine caused a rise; and phenmetrazine had no significant effect. Glucagon, whether given with phenmetrazine or alone, had a significant depressant effect on hunger, when compared with the other drugs and placebo, and on food intake, when compared with placebo.

The New York Hospital
New York, New York

1195 Honigfeld, Gilbert. **Physician and patient attitudes as factors influencing the placebo response in depression.** Diseases of the Nervous System, 24(6):343-347, 1963.

Some determinants of the placebo response were examined in 44 hospitalized depressed patients. Each patient had completed the Attitude Toward Medication Scale (ATM) and the Inpatient Multidimensional Psychiatric Scale (IMPS). Self-ratings by the psychiatrists were made on the Opinions toward Mental Illness Scale (OMI) and the Chemotherapy Attitudes Scale (CAS). The patient and staff attitudes were measured prior to the inception of experimental treatment. The criterion of improvement was the amount of change shown by patients on a specially derived depression scale. The patient's favorable expectancies regarding chemotherapy (ATM scores) were an important determinant of high improvement. The staff attitude measures were also found to relate to improvement; low OMI scores and high CAS scores seemed to favor therapeutic response to placebo. By considering the

characteristic responses of the high- and low-improvement groups, a profile of the ideal therapeutic environment was developed.

Veterans Administration Hospital
Perry Point, Maryland

1196 Niemegeers, Carlos J. E., Verbruggen, Frank J., Van Neuten, Jan M., & Janssen, Paul A. J. **Spiroxamide (R 5188): A new compound producing morphine-like and chlorpromazine-like effects in animals.** International Journal of Neuropharmacology, 2(6):349-354, 1963.

The comparative pharmacology of spiroxamide, dl-8-[2-(1,4-benzodioxanyl)-methyl]-4-oxo-1-phenyl-1,3,8-triaza spiro [4,5] decane, is briefly described in rats, mice, cats, and dogs. Spiroxamide in these animals produces morphine-like lead-pipe rigidity and chlorpromazine-like cataleptic immobility effects. In 10 groups of five rats, each group was given a single s.c. dose, ranging from 0.16 to 80.0 mg/kg (10 different doses). Lead-pipe rigidity is produced in 50% by 2.1 mg/kg spiroxamide and by 7.2 mg/kg morphine. Significant catalepsy is produced in 50% by 4.1 mg/kg spiroxamide and by 5.0 mg/kg chlorpromazine. The morphine-like effects are antagonized by nalorphine, and the chlorpromazine-like effects are antagonized by amphetamine. The s.c. ED_{50}'s of all three drugs that are required to produce morphine-like effects in rats, mice, and cats, as well as chlorpromazine-like effects in rats, mice, and dogs are tabulated. In vitro, spiroxamide is a very weak antihistaminic agent, a weak antagonist of the adrenaline- or noradrenaline-induced contractions of the isolated rabbit spleen, and is devoid of significant anticholinergic activity. The safety margin with s.c. administration in rats and mice is enormous: 640 mg/kg is an atoxic dose in both species, but the lowest effective dose in rats is 25μg/kg body weight, and in mice is 460μg/kg body weight.

Research Laboratory
Beerse, Belgium

See also: 1104, 1133, 1167, 1204, 1207

PHARMACOLOGY

1197 White, Richard P. & Nash, Clinton B. **Catechol antagonism to the EEG effects of reserpine, chlorpromazine, pentobarbital, and atropine.** International Journal of Neuropharmacology, 2(5):249-254, 1963.

This study was made to ascertain the central actions of catechol, using modern techniques. Four phases were conducted: (1) The behavioral actions of 3 to 12 mg/kg catechol alone were noted in unrestrained normal dogs and rabbits and in restrained rabbits from which EEG's were obtained. (2) The EEG and other effects of catechol were observed in adult dogs and albino rabbits under pentobarbital (30 mg/kg) or under artificial respiration following curarization. (3) The EEG and other effects of catechol were observed in rabbits injected 15 minutes after 6 to 12 mg/kg pentobarbital, 5 to 15 mg/kg chlorpromazine, and 2 to 10 mg/kg atropine, and 4 hours after 2 mg/kg reserpine. (4) The EEG and other effects of catechol were observed in rabbits with the neuraxis transected between the midbrain and pontine regions or at cervical segment one and in rabbits with the spinal cord pithed. For comparison, pyrogallol was given to 11 rabbits, and resorcinol was given to 7 rabbits. (All drugs were given i.v. and rapidly.) Catechol alone had no significant effects on blood pressure, but did induce paresis and ataxia. A higher dose of catechol (30 mg/kg) may induce an EEG seizure pattern and a much delayed drop in blood pressure. Catechol evoked EEG alerting in curarized animals, but anesthetic doses of pentobarbital dampened this effect. Catechol reversed the EEG synchrony observed normally or induced by the lesions (Phase 4) and by the CNS depressants (Phase 3). Catechol also antagonized or reduced the behavioral effects of the CNS depressants. Resorcinol (18 mg/kg) and pyrogallol (100 to 200 mg/kg) evoked EEG activation in similar experiments, but pyrogallol failed to produce tremor.

University of Tennessee
Memphis, Tennessee

1198 von Euler, U. S. & Lishajko, F. **Effect of reserpine on the uptake of catecholamines in isolated nerve storage granules.** International Journal of Neuropharmacology, 2(3-4):127-134, 1963.

Because of previous findings that reserpine in high concentrations increases the release of transmitter and in low concentration inhibits the spontaneous depletion of noradrenaline in nerve-storage granules, and that reserpine decreases the uptake of catecholamines in adrenal medullary granules, a similar study was made on isolated nerve granules. Bovine splenic nerve granules were incubated with adrenaline and/or noradrenaline (10μg/ml to 20μg/ml) and with or without reserpine (10μg/ml). Catecholamines were determined fluorometrically. The uptake of added adrenaline or noradrenaline from a suspension of partially depleted adrenergic nerve granules is not inhibited by reserpine 10^{-5} M. Conversely, pretreatment of adrenergic nerve granules with reserpine in phosphate buffer for 1 hour prevents the amine uptake. Undepleted nerve granules, which normally take up added adrenaline through exchange with noradrenaline, fail to do so in the presence of reserpine due to the concomitant block of noradrenaline release.

Karolinska Institutet
Stockholm, Sweden

1199 Hudson, Roy D. & Domino, Edward F. **Effects of chlorpromazine on some motor reflexes.** International Journal of Neuropharmacology, 2(3-4):143-162, 1963.

This study was made to elucidate the site of action of chlorpromazine on the patellar, linguomandibular, and segmental reflexes of cats (adult, both sexes, 2 to 4.6 kg), using six cat preparations. In doses of 1 to 8 mg/kg i.v., the drug produced a significant depression of the patellar reflexes and segmentally evoked potentials in cats with an intact CNS. Hypotension, potentiation of anesthesia, depression of nerve conduction in afferent and efferent nerves, an effect at the neuromuscular junction, or an effect directly on skeletal muscle or muscle spindle were ruled out as mechanisms of reflex

depression. Chlorpromazine caused a significant depression of facilitation and inhibition of the patellar reflex produced by electrical stimulation of the mesencephalic facilitatory and medullary inhibitory areas of the reticular formation. The linguomandibular reflex was also elicited in several preparations. This reflex was significantly depressed in intact and high spinal cats, but the patellar reflex was depressed only in the former. Depression of segmentally evoked potentials was dependent on the intensity of electrical stimulation. The drug was less effective in depressing potentials elicited by supramaximal than by submaximal stimuli (80% of maximum). Mean arterial blood pressure was depressed in all preparations with an intact medullary vasomotor outflow. The site of depression is probably on neurons in portions of the bulbar facilitatory reticular area and, to a lesser extent, on neurons in the bulbar inhibitory reticular area. Chlorpromazine may also act at a spinal level.

University of Michigan
Ann Arbor, Michigan

1200 Karczmar, Alexander G., Blachut, K., Ridlon, S. A., Gothelf, B., & Awad, O. **Pharmacologic actions at various neuroeffectors of single and combined administration of EPN and malathion.** International Journal of Neuropharmacology, 2(3-4):163-180, 1963.

The effects of single and combined administrations of malathion and EPN on CNS and ANS activity, and on neuromuscular transmission were studied in mongrel dogs and spinal cats. Independently of the test employed, EPN exerted its maximal activity within 25 to 35 minutes, whereas the onset of action of effective doses of malathion was almost immediate. The EKG changes were produced with 5 mg/kg of EPN; antagonism of an atropine EEG pattern was occasionally produced at 10 mg/kg, but more often it occurred at 15 mg/kg. Malathion-induced EEG desynchronization occurred only with lethal or supralethal doses. The EPN-malathion combinations produced desynchrony at low doses of the two compounds; antagonism of the atropine pattern could be obtained consistently with effective doses. The EPN, malathion, and their combination increased the responsiveness of all five autonomic neuroeffectors studied; in some cases, blocking actions of these agents and of their combinations were also observed. Both EPN and malathion exhibited widely different potencies from one neuroeffector to another; EPN-malathion potency ratios also varied in this respect. Increase of muscle twitch could be produced consistently by EPN, but not by malathion. Combined administration consistently produced increase of the muscle twitch at low doses of the two compounds. It is suggested that potentiation arising at several neuroeffectors from combined actions of EPN and malathion may depend upon factors other than the interference of one compound with the metabolism of the other.

Stritch School of Medicine
Loyola University
Chicago 12, Illinois

1201 Bloom, F. E., Oliver, A. P., & Salmoiraghi, G. C. **The responsiveness of individual hypothalamic neurons to microelectrophoretically administered endogenous amines.** International Journal of Neuropharmacology, 2(3-4):181-193, 1963.

The responsiveness of individual hypothalamic nerve cells to microelectrophoretically administered acetylcholine (ACh), noradrenaline (NA), and 5HT was investigated. Of the 259 individual cells studied, 98 were found to change their rate of activity in response to one or more of the amines. The ACh-sensitive and NA-sensitive units were encountered more frequently when the electrode traversed the paraventricular and ventral-median nuclei. Nearly equal numbers of ACh-sensitive cells increased and decreased their rate of firing during ACh tests, but the predominant response of NA-sensitive and 5HT-sensitive units was a decrease in rate of firing. It was not possible to predict the direction of the response or the relationship between the responses to different substances. Although most cells responded 5 to 10 seconds after the onset of the test, others responded within 0.5 to 2.0 seconds. Individual variations in onset times of responses were not predictable and were not affected by changes in experimental variables. Return of the discharge rate of sensitive cells to pretest values was relatively fast (2 to 5 seconds) in the case of ACh-sensitive units, but it was generally much slower (2 to 3 minutes) for NA-sensitive and 5HT-sensitive units.

St. Elizabeth's Hospital
Washington, D.C.

1202 Essig, C. F. **Anticonvulsant effect of amino-oxyacetic acid during barbiturate withdrawal in the dog.** International Journal of Neuropharmacology, 2(5): 199-204, 1963.

Thirty-eight beagle dogs were given barbital sodium in single and daily doses that were increased from 40 to 150 mg/kg during 170

days. After abrupt withdrawal of the barbiturate, 16 dogs received only 0.9% saline solution; all had one or more tonic--clonic convulsions during the first 7 days. Nine control dogs died during the first 147 hours of abstinence. Twenty-two dogs received amino-oxyacetic acid (AOAA) every 8 hours from the second to the seventh day of barbiturate withdrawal. Three dosages——5, 8, and 11 mg/kg——were tried. At the lowest dose, two of six animals did not convulse, none developed status epilepticus, and none died. Of the eight dogs that received 8 mg/kg of AOAA, five did not develop convulsions, but two died. Three more dogs died after AOAA was discontinued. At the highest AOAA dose tried, four of eight dogs did not convulse. Four animals, including one that had no convulsions, died. The AOAA induced several episodes of vomiting after nearly every dose. The two higher doses of AOAA caused lethargy and ataxia. The drug did not depress minor signs of barbiturate withdrawal, such as twitching, trembling, or an increased startle response. Hallucinatory behavior was suppressed at the 8 and 11 mg/kg doses.

Addiction Research Center
Lexington, Kentucky

1203 Herz, Albert. **Excitation and inhibition of cholinoceptive brain structures and its relationship to pharmacological induced behaviour changes.** International Journal of Neuropharmacology, 2(5):205-216, 1963.

The effectiveness of atropine-like substances on the electrical activity of the brain was investigated in unanesthetized, curarized rabbits. The following drugs increased the threshold for the induction of EEG arousal and generally caused marked high-voltage, slow-wave activity: scopolamine, Win-12085, benztropine, caramiphen, hyoscyamine, diethazine, aturban, hydroxyzine, captodiamine, beladonnine, chlorpromazine, imipramine, and pentobarbital. With eumydrine, such activity could be observed only after 32 mg/kg. With captodiamine and belladonnine, low-voltage, fast-wave activity was predominant. In 17 experiments, the arecoline doses necessary for the induction of a full arousal reaction varied between 10 and 80 mg/kg; generally, 20 to 40 mg/kg was effective. After the last injection of each test substance, the arecoline dose inducing a complete EEG-arousal reaction was again determined. For atropine-like compounds, the doses required for that effect greatly exceeded the control values. A close linear relationship was found when the inhibition of arecoline analgesia induced by the test substances was compared to the inhibition of the EEG-arousal reaction by the same substances. A similar relationship was observed in regard to potentiation of morphine-induced stupor in rats.

University of Munich
Munich, Germany

1204 Monnier, M., Nosal, Gl., & Radouco-Thomas, C. **Action of analgesics on electrical brain activity, behaviour and nociceptive reaction.** International Journal of Neuropharmacology, 2(5):217-229, 1963.

The effect of meperidine, aminopyrine, acetophenetidin, and acetylsalicylic acid on spontaneous and induced electrical brain activities, on general behavior, and on reaction to electrodental stimulation was investigated in unanesthetized rabbits. Meperidine was tested at 1.5 and 10 mg/kg, i.v.; the nonnarcotic analgesics were tested at 50, 100, 150, 200, and 300 mg/kg, p.o. Meperidine induced sleep-like EEG activity, which decreased within an hour. During this phase, it increased the threshold of the arousal reaction and facilitated the cortical recruiting responses. A waking rebound appeared after 2 hours. Increasing dosages of the nonnarcotic analgesics had progressive excitatory effects: activation of spontaneous electrical brain activity, decreased threshold of arousal reaction, facilitation of cortical responses to stimulation of the arousal reaction to electrical stimulation of the reticular system. Meperidine enhanced transitorily the excitability of unspecific thalamo-cortical projections responsible for the cortical recruiting response. Nonnarcotic analgesics seemed to inhibit the unspecific thalamic system. Both groups of analgesics induced a significant analgesic effect expressed by a rise in the threshold of the nociceptive reaction to electrodental stimulation.

University of Basle
Basle, Switzerland

1205 Pellegrino De Iraldi, Amando & De Robertis, Eduardo. **Action of reserpine, iproniazid and pyrogallol on nerve endings of the pineal gland.** International Journal of Neuropharmacology, 2(5):231-239, 1963.

Drugs affecting the metabolism of catecholamines and indolamines were used to investigate the nature of the granulated vesicles found in adrenergic nerve endings in the pineal gland of the rat. Between 2 and 48 hours after a single 5 mg/kg injection of reserpine, there was an almost complete disap-

pearance of the granulated vesicles. Reserpine action was maximal at 24 hours. Iproniazid (100 mg/kg) produced a moderate increase in the proportion of granulated vesicles, and also in the size of the vesicles and granules. When iproniazid (100 mg/kg) was given i.v. prior to a 5 mg/kg i.p. injection of reserpine, it blocked the release of granulated vesicles caused by reserpine. In rats injected i.v. with repeated 50 mg/kg doses of pyrogallol, there was little or no change in the proportion of granulated vesicles. Pyrogallol did not protect the nerve ending from the action of reserpine.

Instituto de Anatomia General y Embriologia
Buenos Aires, Argentina

1206 Szerb, John C. **Pharmacology. Nature of acetylcholine-like activity released from brain in vivo.** Nature, 197(7871):1016-1017, 1963.

Assays were made on a longitudinal strip of leech muscle and on the blood pressure of an eviscerated cat. Data are tabulated on the activity of 1 ml of brain perfusate (Locke's) and of 1μg γ-butyrobetaine ethyl ester in terms of nanograms of acetylcholine chloride. They show that the activity of Locke's perfusate was similar on the blood pressure of the cat and on leech muscle, but that γ-butyrobetaine ethyl ester was 30 times weaker on the leech muscle. Descending chromatography showed that most of the activity of the perfusate could be recovered at R_f 0.05 to 0.15, where acetylcholine was also found, but that the ester migrated to R_f 0.30 to 0.50. These findings do not give evidence for the release of betaine esters from the brain in vivo, but show that acetylcholine, or a very similar ester, is the transmitter at the cholinergic synapses in the brain cortex.

Dalhousie University
Halifax, Nova Scotia

1207 Curzon, G., Ettlinger, G., Cole, M., & Walsh, J. **The biochemical, behavioral and neurologic effects of high L-tryptophan intake in the Rhesus monkey.** Neurology, 13(1):431-438, 1963.

In this investigation of the effect of tryptophan loading in the presence of iproniazid, two Rhesus monkeys received 0.4% tryptophan plus 0.005% iproniazid phosphate for 2 weeks. One monkey received 0.001% iproniazid for the first 6 days. In a subsequent experiment, three monkeys received 0.4% tryptophan plus 0.005% iproniazid; three control animals received 0.15% glycine plus 0.005% iproniazid; and two controls received only water. Three visual shape-discrimination tests, one spatial-alternation test, and a neurologic examination were made. Determinations of tryptophan, kynurenin, indoleacetic acid, 5-hydroxyindoleacetic acid, etc., were done on 24-hour or bulked 72-hour urines. The monkeys exhibited amino aciduria and excreted elevated amounts of tryptophan metabolites. Changes in complex behavior were not detected, and abnormalities were not apparent upon neurologic examination. When iproniazid was also given, two out of five animals exhibited abnormalities on neurologic examination. Results are discussed in relation to possible biochemical factors in cerebellar ataxia and to the reported behavioral effects on human subjects of tryptophan and iproniazid supplementation.

National Hospital
London, W.C.1, England

1208 Frankenhaeuser, Marianne & Kareby, Sonja. **Effect of meprobamate on catecholamine excretion during mental stress.** Perceptual and Motor Skills, 15:571-577, 1962.

Catecholamine excretion during inactivity, anticipation stress, performance stress, and poststress was compared in two groups of 10 students (20 to 23 years of age). Members of one group received 800 mg meprobamate, and members of the other group received a lactose placebo. During the anticipation and stress periods, subjects were given four tasks that lasted about 6 minutes each. In the poststress period, an informal interview was held. In the placebo group, the excretion of adrenaline and noradrenaline increased during the experiment as compared with baseline values obtained from the inactivity periods. The amount excreted varied with the degree of disturbance. In the meprobamate group, during stress, adrenaline output increased, but noradrenaline output decreased. The difference in noradrenaline excretion between the two groups was significant. The adrenaline excretion was also consistently lower after meprobamate than after placebo, but the difference was not significant. These results indicate that the drug exerted a relatively stronger influence on mild emotional tension, i.e., during anticipation stress, than on more intense reactions, i.e., during performance stress. Thus, meprobamate in moderate doses counteracts the increase in the catecholamine response of normal individuals subjected to mental stress.

Karolinska Institute
Stockholm, Sweden

1209 Martel, R. R., Westermann, E. O., & Maickely, R. P. **Dissociation of reserpine-induced sedation and ACTH hypersecretion.** Life Sciences, 2:151-155, 1962.

The changes in adrenal ascorbic acid, plasma corticosterone, and liver tryptophan pyrrolase (TPO) activity induced by reserpine were compared in control rats and in rats pretreated with the MAO inhibitor pargyline or with desmethylimipramine (DMI). Controls showed the usual response to reserpine: depletion of serotonin and norepinephrine stores, lowering of adrenal ascorbic acid, and elevation of plasma corticosterone levels and of liver TPO activity. In animals pretreated with 25/kg pargyline i.p., none of the characteristic signs of sedation from reserpine were observed, brain amine levels were elevated, and there were no significant changes in levels of adrenal ascorbic acid, of plasma corticosterone, or of liver TPO activity. In animals pretreated with 20 mg/kg DMI i.p. 30 minutes before reserpine, brain amine content dropped, but instead of sedation, the animals exhibited a marked hyperactivity of a "compulsive" exploratory nature. The characteristic signs of pituitary--adrenal stimulation were, however, evident. Results show that pretreatment of rats with an MAO inhibitor blocks the hypersecretion of ACTH as well as the sedative effects induced by reserpine.

McGill University
Montreal, Canada

1210 Lasslo, A., Beasley, J. G., Nelms, G. G., & Epperson, G. J. **The effect of piperidinecarboxamide derivatives on isolated human plasma cholinesterase.** Journal of Medicinal Chemistry, 6(6):811-813, 1963.

A study was designed to investigate the relationships between the molecular constitution, physiochemical characteristics, and biochemical response of several piperidinecarboxamides. The data reported for specific compounds reflect the responses effected by the nature and degree of alkyl substitution on the amido function, the mono- and the corresponding bis(carbamoylpiperidino) substitution on the alkane homologs, the number and arrangement of methylene units in the alkane component attached to the ring nitrogens, and unsaturation in the piperidine ring. With regard to inhibition of cholinesterase, of the monomethyl-, dimethyl-, monoethyl-, and diethylcarbamoyl derivatives evaluated, only the diethyl compound displayed significant inhibitory activity. Except for the 1-methyl-3-(N,N-diethylcarbamoyl) piperidine, the inhibitory activity increased markedly with the chain length of the monosubstituted alkanes. The activity range among the bis-substituted alkanes was not so striking, the decane being not quite seven times as active as the ethane. Among the decanes, the mono-substituted one was the most active, whereas among the ethanes, the bis-substituted compound was the most active. Of all the carbamoylpyridinium analogs studied, only the decyl derivative showed significant inhibition; it was more potent than the corresponding carbamoylpiperidino compound.

University of Tennessee
College of Pharmacy
Memphis, Tennessee

1211 Belleau, B. & Burba, J. **Occupancy of adrenergic receptors and inhibition of catechol O-methyl transferase by tropolones.** Journal of Medicinal Chemistry, 6(6):755-759, 1963.

The role of tropolones as specific inhibitors of catechol-O-methyl transferase (COMT) was investigated. When the effect of a number of synthetic and naturally occurring tropolones on the COMT-catalyzed methylation of norepinephrine was examined, results showed that the presence of ring substituents or their nature had only a marginal effect on the affinity of the tropolone ring for the enzyme. The most active inhibitor of the series was 4-methyltropolone, its affinity for COMT being somewhat greater than that of pyrogallol. Both the amino--imino and the amino--thioxo analogs displayed significant inhibitory activity. Some of the data obtained supported the theory of a chelation mechanism of inhibition. New pharmacological data confirmed that in vivo COMT blockade by tropolones is a competitive inhibition. This fact has now been confirmed by another investigator. In vitro studies showed that catechol and tropolone rings are biochemically isosteric. At 2 mg/kg, β-methyltropolone, 4-(2-amino-1-hydroxy)ethyltropolone, and colchiceine produced a small potentiation of the norepinephrine response (cats); at 4 mg/kg, a readily detectable intensification and prolongation of the response occurred. Colchicine was inactive. The tropolone effect persisted for 2 hours at the 4 mg/kg dose. The affinity of tropolones for adrenergic β-receptors was observed.

University of Ottawa
Ottawa, Ontario, Canada

1212 Thomas, J. **Quaternary ammonium compounds. IV. Antiacetylcholinesterase activity and ring size in aromatic quaternary ammonium compounds.** Journal of Medicinal Chemistry. 6(4):456-457, 1963.

Quinolizinium bromide (I), benzo-b-quinolizinium bromide (II), naphtho[2,1-b]quinolizinium bromide (III), and N-methylpryidinium iodide (IV) were examined for antiacetylcholinesterase activity in order to determine the effect of ring size of the aromatic ion on activity. The biological activities of the compounds were determined by the potentiometric method of Thomas and Marlow. Compound II was the most active, followed in order of decreasing activity by III, I, and IV. Some explanations for the irregular increases in activity are proposed.

University of Manchester
Manchester, England

1213 Brune, Guenter G., Pscheidt, Gordon R., & Himwich, Harold E. **Different responses of urinary tryptamine and of total catecholamines during treatment with reserpine and isocarboxazid in schizophrenic patients.** International Journal of Neuropharmacology, 2(1-2):17-23, 1963.

The purposes of this study were to determine if tryptamine and the total catecholamines would show similar excretion patterns during administration of therapeutic doses of reserpine and/or isocarboxazid, and if correlations exist between behavior and amine excretion. Three groups of male schizophrenics were placed on the following schedules. Group 1 (three patients) received reserpine (15 days), followed by reserpine and isocarboxazid (15 days). Group 2 (seven patients) received reserpine (15 days), the combination (15 days), reserpine (15 days), and placebo (20 days). Group 3 (seven patients) received isocarboxazid for 45 days. Drug doses were constant---4 mg/day reserpine and 30 mg/day isocarboxazid; all were given orally, suspended in water. Reserpine did not change the level of urinary tryptamine unless a change of psychotic behavior occurred. In the latter case, urinary tryptamine followed the same patterns as during placebo administration; i.e., it increased with intensification of psychotic activity. In contrast, during treatment with isocarboxazid alone or in combination with reserpine, the elevation of the urinary level of tryptamine was primarily determined by the action of the MAO inhibitor. Total-catecholamine-excretion patterns differed from those of tryptamine. The drugs had little influence on the urinary levels of catecholamines unless alterations of anxiety, blood pressure, and heart rate occurred. In all instances, decreases or increases of sympathetic activity were followed by corresponding alterations in urinary catecholamines.

Galesburg State Research Hospital
Galesburg, Illinois

1214 Pelz, Kurt S., Gottfried, Sidney P., Clifford, Ruth C., & Paz, Elvira. **Protein fractions in the sera of mentally confused geriatric patients: Effect of corticotropin.** Journal of the American Geriatrics Society, 11(10):983-986, 1963.

This investigation is concerned with the effect of adrenocorticotropin (ACTH) on the protein fractions in the sera of mentally confused elderly people. The response of the adrenal cortex was measured by quantitative determination of the urinary 17-hydroxycorticoids. In the first phase, without ACTH, protein fractions were determined electrophoretically in the sera of 47 men and women past the age of 70 (some were confused and some were mentally alert) and in two control groups---8 mentally alert people over 70 years and 7 mentally alert people under 45 years. The albumin fraction in the sera of the old people, whether mentally confused or alert, was at a significantly lower level than in the younger control gorup. The gamma globulin fraction was at a significantly higher level in the sera of the mentally confused older people than in the mentally alert old people and the younger controls, whereas the $alpha_1$ globulin fraction was lower. In the second phase, 100 units ACTH i.m given to 12 mentally confused old people, 4 mentally alert old people, and 4 younger controls stimulated the adrenal cortex in all, but there was no case of a significant change in the mean values for the serum-protein fractions. Therefore, a change in function of the adrenal cortex apparently was not the cause of the decrease in $alpha_1$ globulin and the increase in gamma globulin in the sera of the mentally confused old people.

The Masonic Charity Foundation
Wallingford, Connecticut

1215 Beernink, K. D., Nelson, S. D., & Mansour, T. E. **Effect of lysergic acid derivatives of the liver fluke fasciola hepatica.** International Journal of Neuropharmacology, 2(3-4):105-112, 1963.

A number of LSD-25 derivatives at various concentrations were compared with respect to their effects on liver-fluke rhythmical

motility. The flukes were suspended in a 15-ml organ bath and attached to a Grass force transducer calibrated to apply a 0.5-g-weight tension. Signals were recorded on a Grass polygraph. Different flukes were used for each concentration tested. The results showed that the compounds had the following order of potency: LSD-25 (most potent), d-lysergic acid (LSA) pyrrolidide, LSA dimethylamide, methyl-LSA diethylamide, LSA monoethylamide, LSA morpholide, 1-methyl-LSA butanolamide, 2-bromo-LSA diethylamide, and 1-LSD-25. All these compounds, except for the last two, had a lower ED_{50} than did 5HT and its derivatives. There is good correlation between the stimulant potency on the liver fluke and the reported hallucinatory effects on man.

Stanford University School of Medicine
Palo Alto, California

1216 Knapp, Donald E. & Domino, Edward F. **Species differences in the EEG response to epinephrine, 5-hydrocytryptamine and nicotine in brainstem transected animals.** International Journal of Neuropharmacology, 2(1-2):51-55, 1963.

A total of 28 brainstem-transected adult animals of both sexes, 10 albino rabbits, 9 cats, 6 Macacus cynamolgus, and 3 Macaca mulatta monkeys were observed for species differences in the EEG activation response to i.v. epinephrine, 5HT, and nicotine. Species differences were found. In midpontine-sectioned rabbits, cats, and dogs and high-pontine monkeys, EEG activation was seen after 10μg/kg to 20μg/kg of nicotine. Similar doses of nicotine also produced EEG. activation in prepontine rabbits and cats but not in the prepontine dog. Also, whereas 4μg/kg to 8μg/kg epinephrine and 30μg/kg 5HT produced EEG activation in the midpontine rabbit and cat, no such response was observed in the midpontine dog or high-pontine monkey. It was also found that a relatively high level of brainstem transection was required to induce a slow-wave EEG pattern in the monkey.

University of Michigan
Ann Arbor, Michigan

1217 Olds, M. E. & Olds, J. **Pharmacological patterns in subcortical reinforcement behavior.** Internationa Journal of Neuropharmacology, 2(6):309-325 1963.

By intercurrent hypothalamic positive reinforcement and tegmental negative reinforcement tests, drug actions on two different brain-stimulated behaviors were assessed simultaneously. Male albino rats were used in the two experiments. The drugs tested were chlorpromazine, meprobamate, d-amphetamine sulfate, and LSD. The experimental procedures are described in detail. Chlorpromazine (2 mg/kg) was effective in antagonizing both hypothalamic positive reinforcement behavior and tegmental negative reinforcement behavior, but it caused a greater percentage deficit in hypothalamic positive behavior. Meprobamate (100 mg/kg) did not produce lasting reduction of hypothalamic positive reinforcement behavior. The findings with LSD and amphetamine were less informative; LSD had a brief suppressing effect on hypothalamic behavior; amphetamine augmented the slow tegmental negative behavior, but it often slowed the rapid hypothalamic positive behavior.

University of Michigan
Ann Arbor, Michigan

1218 Yen, H. C. Y., Sigg, E. B., & Warner, C. L. **Stimulant action of pyridyl derivatives of benzodioxans and benzodioxepans.** International Journal of Neuropharmacology, 2(6):337-347, 1963.

This study is concerned with the structure-activity relationship of related pyridyl derivatives of benzodioxans and benzodioxepans, with particular emphasis on the central stimulant action of GPA 732. (The GPA 732 is N-(4-pyridyl)-1,4-benzodioxan carboxamide.) The following data are tabulated: the chemical structure and pharmacological activity of 24 derivatives in cats and mice; a comparison of pharmacological activities of CNS stimulants in mice; effect of anticonvulsants against pentylenetetrazol, strychnine, GPA 732, and 4-aminopyridine convulsions in mice; effect of convulsants on intact and spinalized frogs; and the CNS activities of amino pyridines and benzodioxancarboxylic and benzodioxepancarboxylic acids. Figures show the effect of topical application of convulsants in the cerebral cortex in cats and the effect of diazepam on seizure discharge induced by GPA 732 in cats. The GPA 732 is a convulsant 6 to 11 times more potent and more toxic than pentylenetetrazol. Its action is of the mixed type, e.g., it precipitates convulsions by blocking inhibitions (strychnine type) and facilitates excitatory synaptic mechanisms (pentylenetetrazol type). Diazepam is the most effective anticonvulsant against seizures induced by GPA 732.

Geigy Research Laboratories
Ardsley, New York

1219 Hosein, E. A. **The isolation of γ-butyrobetaine, crotonbetaine and carnitine from brains of animals killed during induced convulsions.** Archives of Biochemistry and Biophysics, 100:32-35, 1963.

Convulsions were induced in adult albino rats or cats of either sex with i.p. injections of dieldrin (1 g/kg), semicarbazide (400 mg/kg), strychnine (5 mg/kg), sodium fluoroacetate or metrazol (50 mg/kg) in rats, or methionine sulfoximine (15 mg/kg) in cats. Convulsions were also produced in rats by electroshock. When the convulsions were most violent, the animals were decapitated, and the brains were removed for analysis. Reinecke salt precipitation in acid and paper chromatography of the aqueous brain extracts demonstrated the presence of a mixture of γ-butyrobetaine, crotonbetaine, and carnitine. Aqueous extracts prepared from the brains of normal rats or cats, or from animals treated with drugs but killed before convulsions occurred, did not contain any material that was precipitable by Reinecke salt; this material was also absent from the brains of strychnine-convulsed animals.

McGill University
Montreal, Canada

1220 Koll, W., Haase, J., Block, G., & Mühlberg, B. **The predilective action of small doses of morphine on nociceptive spinal reflexes of low spinal cats.** International Journal of Pharmacology, 2(1-2):57-65, 1963.

A cutaneous nerve of the hind limb of decerebrated and spinalized cats was stimulated by electrical square-wave impulses. The ipsilateral nociceptive post δ- and C-flexion reflexes were strongly depressed by 0.3 to 0.4 mg/kg doses of morphine. The morphine effect was evident 20 to 30 minutes after i.v. injection. The nonnociceptive δ-reflex was occasionally depressed, but to a lesser extent. The same doses of morphine had no effect on the nonnociceptive Group II reflex. Small doses (0.02 to 0.06 mg/kg) of nalorphine antagonized the morphine effects. An increase in morphine dosage to 0.05 to 0.6 mg/kg induced a strong and systematic depression of the δ-reflex and, to a lesser extent, the Group II reflex.

Max-Planck-Gesellschraft
Göttingen, Germany

1221 Hsu, Bin & Kin, Kuo-Chang. **Further studies on the pharmacology of tetrahydropalmatine and its analogs.** International Journal of Neuropharmacology, 2(6): 283-290, 1963.

The sedative properties of L-tetrahydropalmatine (L-THP), D-THP, DL-THP, tetrahydroberberine (THB), and rotundine were compared with those of reserpine. The effects of these analogs on evoked potentials and the physiologic diposition of THP were also investigated. Phenelzine (50 mg/kg, twice) pretreatment in mice did not affect the sedative actions of L-THP, DL-THP, THB, or rotundine. When given after phenelzine, reserpine produced extreme excitement and D-THP had no effect. Although THP analogs could effectively antagonize reserpine reversal, they did not alter its long-lasting sedative effects. The D-THP was inactive in this respect. The evoked potentials recorded from the activating reticular formation system were inhibited by L-THP, THB, or rotundine, while those from the cortical sensory or association area remained unchanged. The D-THP often facilitated the cortical primary response. The THP was easily absorbed from the gastrointestinal tract, widely distributed in body tissues, and it readily penetrated the blood--brain barrier.

Academia Sinica
Shanghai, China

1222 Weaver, Lawrence C., Mitchell, Frank E., & Kerley, T. Lamar. **Toxicopathologic and pharmacologic properties of piperacetazine, a potent tranquilizing agent.** Toxicology and Applied Pharmacology, 5:49-60, 1963.

The toxicologic and pharmacologic properties of piperacetazine were investigated. The 24-hour LD_{50} values for piperacetazine in male, Swiss--Webster mice were 820 mg/kg i.g. and 120 mg/kg i.p. In male, Harlan--Wistar rats, the values were 390 mg/kg i.g. and 93 mg/kg i.p. Deaths occurred when dogs received 50 or 200 mg/kg of the drug i.v. In chronic studies, piperacetazine was administered continuously to rats at 0.005%, 0.01%, and 0.025% concentrations of their diets, and daily to dogs at 0.25, 1.0, and 5.0 mg/kg p.o. The drug was well-tolerated by both species; no significant pathologic effects were attributable to the drug. At doses of 2, 20, 40, and 80 mg/kg i.g., piperacetazine did not alter the convulsant properties of pentylenetetrazol. At doses of 2 or 4 mg/kg, piperacetazine sig-

nificantly reduced the fall of mean blood pressure for unusually long periods of time, but it never completely prevented the histamine vasodepression. The drug also reduced, but never prevented, the fall of blood pressure due to acetylcholine injections.

Pitman-Moore Company
Indianapolis, Indiana

1223 Thron, C. Dennis, Patterson, R. N., & Friess, S. L. **Further biological properties of the sea cucumber toxin holothurin A.** Toxicology and Applied Pharmacology, 5:1-11, 1963.

The physical parameters characterizing the low-concentration interaction of the sea cucumber toxin holothurin A with the nodal membrane, with the acetylcholinesterase—acetylcholine (AChE—ACh) system, and with isolated frog sartorius nerve—muscle preparations were investigated. On the single node of Ranvier in frog sciatic nerve, the toxin produced irreversible blockage and destruction of excitability at a limiting lower concentration of 0.01 mg/ml in Ringer's solution. This process is characterized by marked instability of threshold-stimulation voltage and action-current amplitude at intermediate levels of inactivation and by failure to evade the irreversibility of action by simultaneous incubation of the node with much higher concentrations of the reversible blocking agents, eserine or cocaine. Further, the toxin produced no microscopically observable damage to axonal walls or sheaths at neurotoxic-dosage levels. This agent also displays essentially zero inhibitory activity against the purified AChE—ACh system in vitro (at doses as high as 0.5 mg/ml), and produces nonpropagated contracture at the site of topical application to frog sartorius muscle, using 200 mg/ml. These observations are discussed in terms of possible modes of holothurin-receptor interaction.

U.S. Naval Medical Research Institute
Bethesda, Maryland

1224 Karlsberg, Paul, Elliott, Henry W., & Adams, John E. **Effect of various pharmacologic agents on cerebral arteries.** Neurology, 13:772-778, 1963.

This study was conducted with the hope of finding a drug that might be useful in preventing or relieving cerebral arterial spasm in patients with ruptured intracranial aneurysms. Emphasis was placed on the effect of serotonin and/or methysergide. Fifty-six Macacus cynamolgus monkeys of both sexes (2.5 to 6.0 kg in weight) were anesthetized, prepared surgically, and then given the drugs by one of three ways: by a constant-speed infusion pump into the carotid artery, by adding them to the reservoir, or by infusion into the femoral vein. Serotonin proved to be a very potent constrictor and, as such, may play an important role in the etiology of the cerebral vasospasm that follows rupture of intracranial aneurysms. Doses as low as 10μg/kg/minute for 5 minutes almost doubled the perfusion pressure. The same amount of methysergide alone elicited a biphasic systemic response similar to serotonin, but the perfusion pressure passively followed the systemic. The same amount of methysergide antagonized the effects of serotonin administered subsequently, even in doses up to 200μg/kg/minute serotonin. The antagonistic effects lasted 3 hours. In the intact anesthetized monkey, intracarotid infusions of histamine, papaverine, and isoxsuperine, as well as inhalation of 10% carbon dioxide, had strong cerebral vasodilator effects.

University of California School of Medicine
San Francisco, California

1225 Collard, J., Denber, Herman, C. B., & Teller, David N. **The effect of haloanisone upon leucocyte migration.** Diseases of the Nervous System, 24(7):439-441, 1963.

The serial analyses of leucocyte migration in 12 patients who received haloanisone for from 5 to 10 weeks is reported. Haloanisone is 4'-fluoro-4-[4'-(2"-methoxyphenyl)piperazino]butyrophenone. The minimum daily dose was 15 mg, and the maximum dose was 240 mg; the minimum total dose was 765 mg and the maximum dose was 5,515 mg. Leucocyte migration was arbitrarily defined as that distance reached by clumped leucocytes furthest from the original leucocyte layer, as measured from the buffy-coat surface by an oculometer before, during, and after haloanisone treatment. The migration increased progressively during treatment and tended to stabilize after the sixth week. There was no apparent correlation with daily dose, but there was a high correlation with total dose. In conclusion, in vivo treatment followed by in vitro measurement of leucocyte migration appears to indicate a way of measuring drug-penetration rate, drug level in blood, and blood-clearance rate after the drug is

stopped. This may be a possible test of the relative inhibition of phosphorylating or bioenergetic systems by different drugs.

Manhattan State Hospital
Ward's Island, New York

1226 Rockwell, Gaylord H. & Greene, Nicholas M. **Ethamivan and the ventilatory response to carbon dioxide in depressed man.** Clinical Pharmacology and Therapeutics, 4(6):728–733, 1963.

Because the mechanism of analeptics in stimulating respiration is generally unknown, a study was made to evaluate the effect of ethamivan (vanillic acid diethylamide) on the threshold response of the human respiratory center to carbon dioxide. Alveolar carbon dioxide tensions and minute respiratory volumes were measured in five normal subjects (four females and one male, 22 to 48 years of age) prior to the administration of any drug, following elevation of the threshold of the respiratory center to carbon dioxide by large amounts of thiopental (about 15 mg/kg) and up to 100 mg of meperidine given i.v. over a 30- to 50-minute period, and, finally, after a single i.v. injection of 0.75 mg/kg of ethamivan. The effects of ethamivan were tested only in subjects whose respiration had been depressed because of the suggested use of analeptics in such states. The results showed that in the presence of respiratory depression, ethamivan produced a prompt and significant increase in ventilation, but the dosage used did not fully restore ventilation to normal control value. Ethamivan produced this effect by lowering the previously elevated threshold response of the respiratory center to carbon dioxide rather than by inducing hyperventilation through other neurophysiologic mechanisms.

Yale University School of Medicine
New Haven, Connecticut

1227 Loomis, T. A. & Salafsky, B. **Antidotal action of pyridinium oximes in anticholinesterase poisoning; comparative effects of soman, sarin, and neostigmine on neuromuscular function.** Toxicology and Applied Pharmacology, 5:685–701, 1963.

The Warburg technique was used: (1) to evaluate the inhibitor effect of sarin and soman on partially purified AChE and on neuromuscular function; and (2) to compare the effectiveness of some oximes on the effects of soman, sarin, and neostigmine. Soman is a more potent inhibitor of AChE in vitro than sarin. Soman and sarin are equally toxic in the intact rat and are rapidly absorbed after topical application or i.p. injection. The mono- and bis-pyridinium oximes, which are effective antidotes when given with atropine in sarin-poisoned mice, are not effective antidotes in mice poisoned by i.p. injection of two LD_{50}'s of soman. However, mortality of mice poisoned by dermal application of minimal doses of soman is decreased by prior i.p. administration of atropine, the oximes, or a mixture of these agents. Soman produces neuromuscular effects in intact and isolated preparations from rats that are similar to those produced by sarin and neostigmine. Potentiation of twitch response to indirectly induced stimuli produced by these AChE agents is accompanied by an oscillatory postaction potential discharge in the muscle cells. Both the potentiated twitch and the afterpotential are abolished by administration of the pyridinium oximes. The sarin-inhibited tetanic response of the intact and isolated nerve muscle preparations of the rat is promptly reversed by the pyridinium oximes. The soman--inhibited tetanic response in the same preparations is only partially reversed by the pyridinium oximes.

University of Washington
Seattle 5, Washington

1228 Forney, Robert B., Hughes, Francis W., Richards, Alice B., & Gates, Paul W. **Toxicity and depressant action of ethanol and hexobarbital after pretreatment with asparagine.** Toxicology and Applied Pharmacology, 5:790–793, 1963.

Two simple measures of the depressant properties of ethanol and hexobarbital were used to study the influence of l-asparagine pretreatment. Sleeping time, immobility time, and toxicity were determined in three groups of 40 Harlan--Wistar male mice (20 to 25 g in weight), respectively. The animals received 1 g/kg l-asparagine s.c. 4 hours and 1 hour before either ethanol (4 g/kg) or hexobarbital (100 mg/kg) i.p. The i.p. 48-hour LD_{50}'s of ethanol or hexobarbital were determined with and without pretreatment with l-asparagine. Pretreatment with l-asparagine enhanced the depressant properties of ethanol and hexobarbital, as measured by sleeping time and immobility, but did not alter the LD_{50}'s significantly.

Indiana University School of Medicine
Indianapolis, Indiana

1229 Fromm, Gerhard H. & Landgren, Sven. **Effect of diphenylhydantoin on single cells in the spinal trigeminal nucleus.** Neurology, 13:34-37, 1963.

Because of the persisting controversy as to the site of idiopathic trigeminal neuralgia and as to the mode of action of diphenylhydantoin in alleviating it, a study was made of the effect of the drug on single neurons in the spinal nucleus of the trigeminal nerve in adult anesthetized cats. Diphenylhydantoin sodium was injected i.v. in a 50-mg/ml solution (10 to 15 mg/kg of body weight). The latency of response of single neurons to electrical stimulation of the maxillary nerve was markedly increased, reaching a peak 1 to 5 minutes after injection and then gradually waning over the next 40 minutes. At the same time, the postsynaptic focal potential was decreased in amplitude. The latency and the amplitude of the presynaptic spike, however, were only minimally affected. The intrepretation of this is that diphenylhydantoin has an inhibiting effect on synaptic transmission that is probably more significant than its effect on peripheral-nerve conduction and excitability. This is discussed in relation to the theory that idiopathic trigeminal neuralgia is a disease of brain-stem structures rather than of the peripheral nerve.

Tulane University School of Medicine
New Orleans 12, Louisiana

1230 Frawley, J. P., Weir, R., Tusing, T., DuBois, K. P., & Calandra, J. C. **Toxicologic investigations on Delnav.** Toxicology and Applied Pharmacology, 5:605-624, 1963.

The toxicological properties of Delnav, an organic phosphate pesticide consisting of 70% cis and trans isomers of 2,3-p-dioxanedithiol-S,S-bis-(0,0-diethyl phosphorodithioate) as the principal ingredient, were determined to permit recommendations for safe handling during manufacture and use, and to evaluate the safety of residues of Delnav on edible crops. Toxicities were measured in chickens, mice, rats, and dogs by various routes of administration. The acute oral toxicities of 15 other pharmacologically related pesticides alone and in combination with Delnav are tabulated. Anticholinesterase activity was tested in humans. Human volunteers also received Delnav with malathion p.o. to test possible potentiation.

Hercules Powder Company
Wilmington, Delaware

1231 Loomis, T. A., Welsh, M. J., Jr., & Miller, G. T. **A comparative study of some pyridinium oximes as reactivators of phosphorylated acetylcholinesterase and as antidotes in sarin poisoning.** Toxicology and Applied Pharmacology, 5:588-598, 1963.

Five bis-pyridinium oximes with the benzene ring as part of the group connecting the two quaternary nitrogen atoms, two compounds containing aliphatic connecting groups, and a tris-pyridinium oxime were synthesized and tested for: (1) reactivating effect on sarin-inhibited acetylcholinesterase; (2) acute lethal toxicity in mice; (3) effect on sarin-inhibited neuromuscular function in rabbits; and (4) effect on sarin-potentiated, vagus-induced bradycardia in rabbits. The results showed a range of activity as reactivators of phosphorylated acetylcholinesterase that varied from activity greater than that of 1-methyl-2-formylpyridinium oxime (PAM-2) to less than that of PAM-2. When compared with PAM-2, the benzene derivatives showed greater toxicity as determined by the LD_{50}, but only the para-benzene derivatives showed greater potency in producing recovery of sarin-inhibited neuromuscular function. The tris compound showed relatively high reactivator potency in vitro and showed relatively high toxicity and potency in vivo.

University of Washington School of Medicine
Seattle, Washington

1232 Norden, Leo G. & Plaa, Gabriel L. **Interaction between sodium bromide and chlorpromazine.** Toxicology and Applied Pharmacology, 5:437-444, 1963.

A possible interaction between bromides and chlorpromazine was investigated in male albino mice. Chlorpromazine-induced sleeping times in mice after pretreatment with sodium bromide were compared to those in mice which had not been pretreated. Pretreatment doses of sodium bromide varied from 125 mg/kg to 1.0 g/kg; the chlorpromazine doses were from 5 to 20 mg/kg. Rectal temperatures were taken to determine the effect of sodium bromide on chlorpromazine-induced hypothermia. The effect of sodium bromide on the LD_{50} of chlorpromazine was also studied. The anticonvulsant effect of the doses of sodium bromide employed was assessed against maximal electroshock seizures and pentylenetetrazol. Chlorpromazine-induced sleeping time was increased by bromide; the effect was both time and dose dependent. A plasma bromide concentration above 65 mg% is required before enhanced depression becomes evident by gross observa-

tion. The effect on sleeping time seems to be relatively specific, since neither the acute lethal potency of chlorpromazine nor the hypothermic response was enhanced by bromide pretreatment.

State University of Iowa
College of Medicine
Iowa City, Iowa

1233 Greer, Melvin & Williams, Clyde M. **Dopamine metabolism in Parkinson's disease.** Neurology, 13:73-76, 1963.

To determine whether a biochemical defect in dopamine metabolism exists in patients with Parkinson's disease, the urinary excretion of homovanillic acid (HVA), the major terminal metabolite of dopamine, was measured in patients with Parkinson's disease and compared with the excretion in normal subjects. Twenty patients with parkinsonism (46 to 71 years of age) and 17 control subjects, in the same age group, who had no neurological disease were used in the study. Urinary excretion of HVA was not significantly different in the two groups. The excretion of HVA following the administration of reserpine and of DOPA was also similar in both groups. No significant clinical effect was apparent after drug administration in either group. It is concluded that there is no abnormality in overall metabolism of dopamine in patients with parkinsonism, but the possibility of a local aberration in dopamine metabolism in the corpus striatum cannot be excluded.

University of Florida College of Medicine
Gainesville, Florida

1234 Pineda, Anselmo & Snider, Ray S. **Nonspecific depressant action of serotonin on brain stem and cerebellum.** Neurology, 13:166-176, 1963.

The action of 5HT on the evoked response was investigated at different levels of the brain stem and on the surface of the cerebellum and cerebrum. Twenty-two cats (1.8 to 3.66 kg in weight) were used in the study. Standard doses of 5HT (10 g) were given by the following routes of administration: cerebellomedullary cistern, lateral ventricle, or contralateral or ipsilateral carotid arteries in the neck. The serotonin precursor, dl-5-hydroxytryptophane, was given i.v. in the hindlimb in amounts up to 50 mg. Serotonin caused a depressant effect on evoked potentials in the cerebellum and cerebrum following peripheral nerve stimulation. This effect was present in the following thalamic nuclei: ventroposterolateralis, ventrolateralis, medialis dorsalis, centralis lateralis, and centrum medianum. There was a prolonged delay of action or else no effect in the mesencephalic reticular formation. When higher doses were used (20μg/kg to 40μg/kg), the animals suffered from respiratory arrest. When artificial respiration was used, there was first a diminution of amplitude, then a total reappearance of the evoked response. The evoked responses returned to normal before the respiratory system was active enough to maintain respiration. These data are interpreted to indicate that serotonin has a general nonspecific effect on the CNS.

Northwestern University Medical School
Chicago, Illinois

1235 Ivanov, Yu. N. & Semeyko, Ye. I. **Changes in the stereotype of conditioned respiratory reflexes and respiratory responses to CO_2 under the influence of chlorpromazine.** Zhurnal Vysschey Nervnoi Deyatelnosti, 13(4):680-685, 1963.

The effect of small doses of chlorpromazine on the respiratory responses was studied to elucidate the mechanism of action of the drug on the CNS. Two series of chronic experiments were run on dogs. In the first series, the respiratory responses to the action of a 2.5% to 3% CO_2 mixture in air were measured in normal dogs and in dogs deprived of the three pairs of distance receptors before and after injection of 2 to 3 mg/kg chlorpromazine. In the second series, the effect of chlorpromazine on the course of conditioned and unconditioned respiratory responses was studied. Changes in the sensitivity of the respiratory responses to CO_2 under the influence of small doses of chlorpromazine are considerably smaller in dogs deprived of the three pairs of distance receptors. Under chlorpromazine, the respiratory conditioned reflex is the first to be disrupted; the unconditioned respiratory response is retained for a longer time. Recovery of responses occurs in reverse order. The cerebral cortex appears to be the primary site affected by small doses of chlorpromazine.

Office of Technical Services
U.S. Department of Commerce
Washington, D.C.

1236 Rowe, George G., Afonso, Skoda, Castillo, Cesar A., Kyle, John C., Leicht, Thomas R., & Crumpton, Charles W. **Systemic and coronary hemodynamic effects of an amine oxidase inhibitor and of serotonin.** Clinical Pharmacology and Therapeutics, 4(4):467-475, 1963.

The systemic and coronary hemodynamic effects of pheniprazine, an active amine oxidase inhibitor, were studied in dogs on both acute i.v. administration (2.5 mg/kg) and after an 18-hour pretreatment period with the drug. Studies were also made of the hemodynamic effects of serotonin in dogs pretreated with pheniprazine, and the effects of serotonin given in the left atrium were determined in a control series of dogs. No significant hemodynamic changes occurred, although the arterial hemoglobin and hematocrit rose and the body oxygen consumption tended to be higher after pheniprazine. The hemodynamic effects of serotonin were slightly increased after pheniprazine pretreatment in that the cardiac rate increased more, the arterial pressure decreased further, and left ventricular work was reduced. When injected in the same dose into the left atrium of control animals, serotonin produced a response qualitatively similar to that during its right atrial administration. The relation of the present observations to the pathogenesis of the carcinoid syndrome and to the therapy of angina pectoris is discussed.

University of Wisconsin Medican School
Madison, Wisconsin

1237 Natelson, Samuel, Pincus, Joseph B., & Rannazzisi, Gandolfo. **Dynamic control of calcium, phosphate, citrate, and glucose levels in blood serum. Effect of ACTH, adrenaline, noradrenaline, hydrocortisone, parathormone, insulin, and glucagon.** Clinical Chemistry, 9(1):31-62, 1963.

The effect of ACTH (2 U/kg), adrenaline (01 mg/kg), noradrenaline (0.1 mg/kg), insulin (0.25 U/kg), parathormone (100 U/kg), hydrocortisone (6 to 20 mg/kg), and glucagon (0.14 mg/kg) on the homeostatic mechanism controlling serum glucose, citrate, calcium, phosphorus, and potassium was studied in fasting male rabbits (3 to 4 kg in weight) and in male and female children (9 months to 6 years old) who were either normal or had hormone aberrations. There were 8 children in each group, and 5 to 11 rabbits were used per drug. All drugs were given i.m. except insulin, which was given s.c. Citrate levels were kept in balance by ACTH, adrenaline, and glucagon, which raised the levels, and by insulin, which lowered them. Stress alone raised citrate levels, probably through adrenaline and ACTH effects. Glucagon and adrenaline were the immediate factors for raising glucose levels, and insulin was the counterbalancing force. Calcium levels in rabbits were markedly lowered by ACTH. Adrenaline had a similar but milder effect. Parathormone raised calcium levels slowly. Insulin, adrenaline, ACTH, glucagon, and parathormone lowered phosphate levels in the rabbit; only noradrenaline caused a significant rise. In the normal child, only citrate moved in the same direction (elevated) as in the rabbit after ACTH. Children with CNS abnormality behaved like normal children except for three with febrile convulsions. In conclusion, homeostatic control of the constituents studied may be accomplished by a balance of hormonal factors.

Pediatric Department of New York State Medical School
New York, New York

1238 Warren, Kenneth S. & Schenker, Steven. **Drugs related to the exacerbation or amelioration of hepatic coma and their effects on ammonia toxicity.** Clinical Science, 25:11-15, 1963.

This study was made in an attempt to determine whether drugs having a harmful or beneficial effect on hepatic coma had the same effects on ammonia toxicity. The toxicity of i.v. ammonium chloride was determined in female Swiss albino mice (18 to 22 g in weight) before and after administration of high dosages of 12 drugs. At the time of maximal action of each drug, 1 ml of 0.9% sodium chloride containing ammonium chloride in various concentrations (400 to 1,300 mg/100 ml) was injected into the tail vein during a time interval of about 2 seconds. Five to 20 animals were used for each of three to six concentrations of ammonium chloride. Of the 12 drugs tested, four (cortisone, paraldehyde, morphine, and 5HTP) had no effect; seven drugs (monosodium glutamate, phenobarbital, iproniazid, pentobarbital, acetazolamide, arginine monohydrochloride, and chlorothiazide) provided protection; and one drug (formaldehyde) exacerbated acute ammonium chloride toxicity. Thus, formaldehyde was the only drug that was related to an increase in ammonium chloride toxicity. In conclusion, there seems to be no direct relation between drugs that exacerbate hepatic coma and their effects on ammonium chloride toxicity.

National Institutes of Health
Bethesda 14, Maryland

1239 De Bono, E., De J. Lee, G., Mottram, F. R., Pickering, G. W., Brown, J. J., Keen, H., Peart, W. S., & Sanderson, P. H. **The action of angiotensin in man.** Clinical Science, 25:123-157, 1963.

The action of synthetic angiotensin on the circulation of man, which may be of importance in understanding the control of circulation in normal and hypertensive subjects, is reported. Synthetic angiotensin I (isoleucine 5) and angiotensin II (valine 5) octapeptides were dissolved in 9.9% saline with heparin (50 U/ml) and then given to normal and hypertensive subjects as a slow infusion (2μg/minute to 6μg/minute) or in a single injection (5μg to 15μg). Both octapeptides seemed to have equal potency and similar actions in man. When infused i.v., they were, weight for weight, 6 to 8 times as potent and, molecule for molecule, 40 to 50 times as potent as noradrenaline in raising arterial pressure. Angiotensin infused i.a. reduced blood flow through the forearm and hand; it constricted muscle and skin vessels. Infused i.v., it produced rise of systolic, diastolic, and mean pressures; slowing of the heart; reduction in cardiac output (stroke volume being unchanged); increased right atrial pressure; no change or slight increase in heart size; slight decrease in intrathoracic blood volume; rise of pulmonary-artery and pulmonary-wedge pressures; increased skeletal-muscle blood flow; decreased skin flow in a comfortably warm subject, increased hand flow in a hot subject; decreased liver blood flow; and decreased glomerular filtration rate, effective renal plasma flow, urine flow, and sodium, potassium, and chloride excretion. Angiotensin is compared with adrenaline and noradrenaline in circulation-pattern changes. The relevance of these observations to the function of angiotensin and its role in hypertension are discussed.

University of Oxford
Oxford, England

1240 Thron, C. Dennis, Durant, R. C., Patterson, R. N., Reber, L. J., & Friess, S. L. **Further elements of structural specificity in potentiation and blockade of excitable tissue preparations by aryl esters of tropine and ψ-tropine. III.** Toxicology and Applied Pharmacology, 5:79-104, 1963.

The roles of the diphenylacetate, o-chlorophenylacetate, m-chlorophenylacetate, p-chlorophenylacetate, and p-tolylacetate esters of tropine and pseudotropine in excitation and blockade at the level of the single node of Ranvier in frog sciatic nerve, the phrenic nerve--diaphragm preparation from the rat, the purified acetylcholinesterase--acetylcholine (AChE--ACh) system in vitro, and, in part, at the whole-body level as intravenously administered toxins in the mouse or cat are described. The entire ester series functions as weak-to-moderate AChE inhibitors. The esters are potent blocking agents on the single node of Ranvier; two p-chlorophenylacetate esters, which produce slight increases in action current at high concentrations (20 mM), are striking exceptions. On the rat phrenic nerve--diaphragm, the esters generally evoke striking potentiation of muscle twitch response at low concentrations and blockade of twitch response as the concentrations are raised. In the intact mouse and cat, the agents are potent convulsants. These findings are discussed in terms of possible modes of drug--chemoreceptor interaction in the biological preparations studied.

National Naval Medical Center
Bethesda, Maryland

1241 Glassman, Jerome M., Dervinis, Alphonse, Beckfield, William J., & Seifter, Joseph. **Acute and chronic toxicity of oxethazaine: A highly potent local anesthetic.** Toxicology and Applied Pharmacology, 5:184-200, 1963.

Acute and chronic toxicity studies were run on the local anesthetic oxethazaine; C^{14}-labled oxethazaine was used for absorption and excretion studies. Acute toxicity studies established that the drug does not cause skin irritation, corneal damage, conjunctival erythema, or hyperemia. There is a considerable margin of safety for intragastric, subcutaneous, intramuscular, intrarectal, and intravesical administration. Toxicity following intravenous and intrapulmonary administration is high. Rats and dogs can ingest oxethazaine daily for months without evidence of either toxicity, effect on weight, peripheral blood picture, bone marrow, viscera or kidney, and liver function. Absorption of intragastrically administered oxethazaine in water or alumina gel occurs rapidly and is detectable within 30 minutes. The amounts absorbed, however, differ and are greater from the water vehicle. Detoxication probably is chiefly in the liver and involves the metabolism of hydroxyethylamine and mephentermine.

Wyeth Laboratories, Inc.
Radnor, Pennsylvania

1242 Sigg, E. B. **Pharmacology of (2-benziloxyethyl)dimethyl (N-octyl)-ammonium bromide, a new spasmolytic agent.** Toxicology and Applied Pharmacology, 5:225-234, 1963.

The musculotropic and spasmolytic properties of the dimethyl octyl ammonium ester of benzilic acid (AD-205) were compared to those of atropine, adiphenine, and papaverine. The acute toxicity of AD-205 was determined by administering the agent i.v., s.c., p.o., and i.p. in mice and i.v. in dogs. Isolated tissue studies included spasmolytic effect on guinea-pig rectum, and vasodilator activity on perfused rabbit-ear preparation. The broncholytic effect was studied in guinea pigs. Gastrointestinal motility was tested in dogs and cats; reduction of the height of bladder contractions after stimulation of the pelvic nerve was calculated in female dogs. The mydriatic effect of AD-205 as compared to atropine was studied in mice after i.p. and p.o. administration. The AD-205 possessed marked anticholinergic properties. The mydriatic effect of the drug was 50 times less than that of atropine after parenteral administration. The oral toxicity in mice was 1,150 mg/kg, which is lower than that of atropine and adiphenine.

Geigy Research Laboratories
Ardsley, New York

1243 Delahunt, C. S., O'Connor, R. A., Yeary, R. A., & Kuwabara, T. **Toxic retinopathy following prolonged treatment with dl-(p-trifluoromethylphenyl) isopropylamine hydrochloride (P-1727) in experimental animals.** Toxicology and Applied Pharmacology, 5:298-305, 1963.

As part of a study to assess possible adverse effects of para-trifluoromethylphenyl isopropylamine hydrochloride (P-1727), ocular damage from chronic administration of the drug in rats and dogs was investigated. Weanling rats of both sexes were given oral doses of 10, 25, or 50 mg/kg P-1727 daily, 6 days per week for 12 weeks. Dogs received oral doses of 10, 25, or 50 mg/kg daily, 6 days per week. Two control groups of two dogs each received 10 and 5 mg/kg/day of amphetamine for 3 months. Another group of six dogs served as normal controls. One-third of treated dogs were killed after 3 month's chronic administration, and the remaining dogs were killed at 6 months. Ophthalmoscopic examinations were done periodically. Eye sections were examined histologically. The P-1727 caused blood-vascular changes in the posterior compartment of rats' and dogs' eyes. The extent of damage depended on dose and duration of treatment. It is believed that the anoxia resulting from the vascular changes in the retinochoroid area produced degeneration of the visual receptors and a pigmentary proliferation.

Chas. Pfizer & Co., Inc.
Groton, Connecticut

1244 Borison, H. L., McCarthy, L. E., Clark, W. G., & Radhakrishnan, N. **Vomiting, hypothermia, and respiratory paralysis due to tetrodotoxin (puffer fish poison) in the cat.** Toxicology and Applied Pharmacology, 5:350-357, 1963.

To reveal possible central respiratory depressant action of tetrodotoxin, the poison was given to chronic cats by intracerebroventricular, intravenous, and intracisternal injection. The toxin evoked vomiting after intravenous administration, but not when given by the other routes. Ablation of the medullary emetic chemoreceptor trigger zone (CTZ) abolished the vomiting response. Intraventricular injection of tetrodotoxin, in doses from 1/250 to 1/500 of the intravenous requirement, caused volitional paralysis, hypothermia, and respiratory failure; pinna, corneal, and deep tendon reflexes remained active. These effects are attributed to an action of the toxin on paraventricular brainstem structures since intracisternal injection failed to elicit any notable response. In acute experiments, respiratory failure due to intraventricular tetrodotoxin was characterized by loss of sensitivity to CO_2 and development of apneustic breathing; the medullary integrating mechanism continued to respond to stimulation after respiratory arrest.

University of Utah College of Medicine
Salt Lake City, Utah

1245 Friess, S. L. & Durant, R. C. **Interference patterns in twitch potentiation of the rat phrenic nerve-diaphragm by aryl esters of tropine and ψ-tropine.** Toxicology and Applied Pharmacology, 5:358-370, 1963.

Enhancement of twitch amplitude in rat phrenic nerve--diaphragm preparation by pairwise incubation with isomeric mixtures of the p-tolylacetate esters of atropine and pseudotropine, and with mixtures of the isomeric o-chlorophenylacetates was studied. The stimulus pattern involved the produc-

tion of paired twitch responses indirectly via the phrenic nerve and directly via muscle stimulation, with a 3-second interval between these stimuli and a 10-second cycle on repetition. Drug concentrations were restricted to levels at which twitch potentiation was the sole drug-induced phenomenon. With the p-tolylacetates at equimolar mixture, mixing the agents produced a degree of amplitude enhancement that was considerably less than that summed for the components acting independently. Such a diminution in total potentiating effect was also noted for an equimolar mixture of structurally dissimilar agents (tropine p-tolylacetate and caffeine) acting conjointly. The diminution in potentiation values for the 50:50 mixture acting on the unblocked nerve—diaphragm preparation is completely eliminated in the directly elicited twitch response when the synapse is blocked with d-tubocurarine ion. Results are discussed in terms of the Waser pore model for the postsynaptic membrane.

National Naval Medical Center
Bethesda, Maryland

1246 Balazs, T. & Grice, H. C. **The relationship between liver necrosis and pentobarbital sleeping time in rats.** Toxicology and Applied Pharmacology, 5:387-391, 1963.

Prolongation of pentobarbital sleeping time (PST), serum glutamic pyruvic transaminase (SGPT) level, icterus index, and morphologic changes were used to examine the relationship between hepatic injury and metabolic liver function. Rats of both sexes weighing 120 to 140 g were used. The hepatotoxins used, the dose per 100 g body weight, and the route of administration were as follows: 0.4 ml CCl_4 s.c., 5 mg of 2% aqueous allyl alcohol solution p.o., and 2.5 and 5 mg of 2% aqueous dimethylnitrosamine solution p.o. The CCl_4 and 5 mg/100 g dimethylnitrosamine caused evenly distributed zonal necrosis and increased all test values. Dimethylnitrosamine (2.5 mg/100 g) produced disseminated centrilobular necrotic foci and increased PST and SGPT but not the icterus index. Allyl alcohol induced massive necrosis confined to some lobes; it increased the SGPT level but not the PST or the icterus index. These findings indicate that jaundice and prolongation of PST are not a cause and effect relationship, and that the PST test should not be relied upon as the sole method for assessing liver injury in toxicity studies.

Department of National Health and Welfare
Ottawa, Ontario, Canada

See also: 1068, 1069, 1070, 1072, 1073, 1103, 1108, 1117, 1133, 1134, 1144, 1146, 1147, 1150, 1152, 1157, 1162, 1167, 1174, 1194, 1248, 1249, 1250, 1251, 1252, 1253, 1255, 1256, 1257, 1259, 1261, 1262, 1265, 1266, 1269, 1272, 1273, 1275, 1277, 1280, 1281, 1282, 1283, 1286, 1293, 1294, 1295, 1297, 1300, 1306, 1309, 1210, 1311, 1313, 1314, 1315, 1316, 1317, 1318, 1320, 1321, 1322, 1323, 1324, 1325, 1326, 1328, 1330, 1331, 1332, 1333, 1334, 1335, 1336, 1337, 1339, 1340, 1341

BIOCHEMISTRY

1247 Eichhorn, F. & Rutenberg, A. **A simple low-voltage paper electrophoretic method for the determination of urinary vanillylmandelic acid (VMA).** Clinical Chemistry, 9(5):615-619, 1963.

A simple and accurate method for the determination of urinary 3-methoxy-4-hydroxymandelic acid, vanillyl-mandelic acid (VMA), is described. The separation of VMA from all other phenolic acids in an approximately 0.05-ml sample of untreated urine is achieved by low-voltage paper electrophoresis with two different buffer concentrations---one for the cathode and one for the anode. The VMA appears as a purple band after staining of the strip with a diazo mixture. The band is eluted and read in a colorimeter. The method was used with 180 urine samples; data on pathologic VMA levels in eight patients are tabulated.

Beilinson Hospital
Petah Tiqva, Israel

1248 Lehr, H., Randall, L. O., & Goldberg, M. W. **Substituted 2-mercaptoisobutyramides and 2-ethyl-2-mercaptobutyramides.** Journal of Medicinal Chemistry, 6(4):351-355, 1963.

A series of S- and N-substituted 2-mercaptoisobutyramides, 2-ethyl-2-mercaptobutyramides, and their corresponding sulfones were synthesized and then evaluated pharmacologically. Sedative and hypnotic effects were evaulated in mice. Effectiveness in protecting against convulsions from pentylenetetrazole or electroshock was measured as were antistrychnine effect and toxicity. Gross behavioral effects were observed in cats, dogs, and monkeys following oral administration of large doses. The S-substituted 2-mercaptoisobutyramides had relatively weak activity as sedatives, hypnotics, and anticonvulsants in mice and as ataxia-inducing agents in cats. Considerably greater activity was observed in the S-substituted 2-ethyl-2-mercaptobutyramides; the propargyl, allyl, methyl, ethyl, and propyl derivatives all had sedative, hypnotic, and anticonvulsant effects well below the lethal dose in mice. At moderate dose levels, they caused ataxia and weakness in cats. The propargyl derivative caused ataxia and sleep in dogs at 80 mg/kg p.o., with a duration of 3 to 4 days. Under the same conditions, the allyl derivative induced ataxia and sleep, which persisted for 24 hours. Monkeys showed marked ataxia at the same dose level. The sulfones showed very little activity as CNS depressants.

Hoffmann-La Roche Inc.
Nutley, New Jersey

1249 Whittle, B. A. & Young, E. H. P. **The synthesis and pharmacological activity of some chloro-α-alkyltryptamines.** Journal of Medicinal Chemistry, 6(4):378-380, 1963.

Eight monochloro analogs of α-methyl- and α-ethyltryptamines were prepared and examined for cardiovascular and CNS activity. All eight compounds were less active than α-methyltryptamine as MAO inhibitors and in their antireserpine activity. The 5-chloro-α-methyl compound was the most effective in protecting against electroshock convulsions in rats. There appeared to be little correlation between in vitro activity against either enzyme and anticonvulsant or stimulant activity. The 5-chloro-α-methyl and the 5-chloro-α-ethyl compounds caused marked behavioral changes in conscious cats. At doses of 5 mg/kg, the animals showed signs of sympathomimetic stimulation including defensive hostility associated with piloerection, exophthalmos, and arched back. Extreme pupillary constriction was seen with 5-chloro-α-methyltryptamine.

Imperial Chemical Industries Ltd.
Cheshire, England

1250 Cignarella, Giorgio, Occelli, Emilio, Maffii, Giulio, & Testa, Emilio. **Bicyclic homologs of piperazine. V. Synthesis and analgesic activity of 3-methyl-3,8-diazabicyclooctane derivatives.** Journal of Medicinal Chemistry, 6(4):385-387, 1963.

A series of 8-alkyl-8-aralkyl- and 8-acyl-substituted 3-methyl-3,8-diazabicyclo[3.2.1] octanes were synthesized for pharmacological screening. The 8-acyl-substituted compounds

showed a significant analgesic activity. When injected i.p. in rats, 3-methyl-8-propionyl-3,8-diazabicyclo[3.2.1]octane was the most active of the series. Its analgesic activity was retained by oral administration. When the propionyl group was replaced by other acyl groups, activity decreased sharply; the carbomethoxy, carbethoxy, and phenylcarbamoyl groups gave products that were minimally active. All the 3-acyl-8-methyl isomers were inactive as analgesics. The only other significant activity found among the tested compounds was the marked local anesthetic action of 8-[β-ethyl-3-methyl-3,8-diazabicyclo[3.2.1]octane] p-aminobenzoate trihydrochloride. Its activity was comparable to that of the corresponding 8-methyl isomer and to that of procaine.

Lepetit S.p.A.
Milan, Italy

1251 Teller, David N., Goldberg, Brenda, & Denber, Herman C. B. **Methods of early drug evaluation--I. Leucocytic motility and succinic dehydrogenase activity.** International Journal of Neuropharmacology, 2(5): 241-247, 1963.

The effects of oral thioproperazine upon leucocyte migration and leucocytic succinic dehydrogenase activity are compared with blood levels and cumulative dose during therapy in female psychotic patients. For in vitro drug effects, 5 to 10 ml of heparinized blood were drawn, centrifuged, washed, etc., and a suspension of 10^6 white cells/ml 0.25 M sucrose was used for assay purposes. Succinic dehydrogenase (SDH) and ascorbate--cytochrome c oxidase were determined, using the manometric method of Potter. Oxygen consumption by leucocytes before and after drug addition (100 times initial therapeutic dose) was recorded and compared to the respiration of untreated cells. If there was no difference, the concentration was increased (1,000 times initial dose) or vice versa. In vivo drug toxicity was determined in five patients given 4 to 40 mg/day of drug. Leucocyte migration, enzyme activity, and plasma drug levels were determined. Migration and oxygen uptake by leucocytes increased in vitro after in vivo treatment. A pronounced lag between the initiation of the drug and the response of these two parameters occurred. Peak plasma drug level corresponded to maximal cumulative dose, but peak migration rate corresponded to maximal increase in SDH oxygen uptake. These two easily performed measurements of drug effect indicate delayed recovery and/or delayed tissue clearance after medication stops and indicate the rate of cumulative response during treatment.

Manhattan State Hospital
New York, New York

1252 Kravitz, E. A., Kuffler, S. W., & Potter, D. C. **Gamma-aminobutyric acid and other blocking compounds in crustacea. III. Their relative concentrations in separated motor and inhibitory axons.** Journal of Neurophysiology, 26(5):739-751, 1963.

In previous experiments, GABA was measured in several peripheral nerves and found to be in highest concentration in a nerve that contained only one motor and one inhibitory axon. The present work was done to determine if GABA was specifically concentrated in the inhibitory axon. Two efferent axons of similar diameter, one inhibitory and the other excitatory, run side by side in the lobster leg (Homarus americanus). Long, unbranched stretches of these neurons were removed and separated; the isolated axons were analyzed for their content of GABA and nine other synaptic blocking compounds that had been found previously in the crustacean nervous system. Two types of experiments were performed. The first was to compare GABA contents enzymatically, and the second was to compare the concentrations of the blocking agents chromatographically or by physiological assay. The GABA content along the course of the inhibitory axon was about 0.5% of its wet weight, but no GABA was found in the accompanying excitatory fiber. The GABA may therefore be confined to inhibitory nerves. The other blocking compounds, with the possible exception of β-alanine (a much weaker blocking agent than GABA), were found in both neuron types. (The distribution of β-alanine cannot be stated positively.) It is concluded that GABA has a physiological role specifically confined to inhibitory neurons, as opposed to the other blocking agents, which are present in both fibers.

Harvard Medical School
Boston, Massachusetts

1253 Steiner, William G., Bost, Kathryn, & Himwich, Harold E. **An electroencephalographic study of some structural aspects of d-amphetamine antagonism in phenothiazine and related compounds.** International Journal of Neuropharmacology, 2(6):327-335, 1963.

The purpose of this experiment was to determine if certain types of substitution or rearrangement of chemical structure would ma-

terially alter the sympatholytic activity of phenothiazines and related nonphenothiazines. A total of 65 adult New Zealand male albino rabbits (3 kg in weight) were tracheotomized, curarized, and artifically respired prior to the administration of one of 26 drugs studied. Monopolar EEG recordings were taken from the cortex, caudate nucleus, thalamus, hippocampus, amygdala, and the reticular substance just cephalad to the pons. Histological examinations were not made. The drugs were evaluated according to their ability to reverse d-amphetamine-induced EEG alerting or their ability to maintain a state of EEG synchrony in the presence of amphetamine. Reversing drugs were given by the femoral vein, 1.0 mg/kg every 4 minutes, after an initial EEG arousal pattern produced by 5.0 to 6.0 d-amphetamine. The EEG synchrony was maintained in the presence of 9.0 mg/kg d-amphetamine, as measured by blocking the EEG alerting response. The influences of structure on sympatholytic activity found are discussed.

Galesburg State Research Hospital
Galesburg, Illinois

1254 Gothelf, Bernard & Karczmar, Alexander G. **Quantitative colorimetric method and extraction procedure for determination of chlorpromazine in animal tissues.** International Journal of Neuropharmacology, 2(1-2):95-99, 1963.

A procedure for the quantitative analysis of chlorpromazine from biologic tissues is based on the oxidation of chlorpromazine by ferric ion in the presence of an equal volume of concentrated sulfuric acid and on its extraction into alkaline ether. The cherry-red chromophore obtained is read spectrophotometrically and shows an absorption maximum between 520 and 530 mμ. The intensity of color is related to the concentrations of sulfuric acid and ferric ion. At the concentrations of reagents used here, the relationship between chlorpromazine concentration and optical density followed Beer--Lambert's Law over the range of from 1μg/ml to 35μg/ml chlorpromazine. This procedure was used to determine the drug in blood and in homogenates of brain, liver, muscle, and other tissues. A reagent blank of distilled water and standard solutions of 50μg, 100μg, or 200μg of the drug were also analyzed. This method yielded 80% to 90% recoveries of chlorpromazine. It was specific for chlorpromazine and for other 2-chlorophenothiazines possessing a side chain on the ring nitrogen. Color was not present or a different color was obtained with changes in the phenothiazine nucleus and with substitutions for chlorine in the 2 position.

University of Loyola
Chicago 12, Illinois

1255 Maynard, Laurence S. & Schenker, Victor J. **Decarboxylase activity in vivo: Effects of morphine and ethanol pretreatment in mice.** International Journal of Neuropharmacology, 2(6):303-307, 1963.

The effects of morphine and of ethanol pretreatment on the decarboxylation of 5HTP in vivo are reported. The method of decarboxylase assay presented possesses several new features, and it may be applicable to the study of many oxidative processes in vivo. Mice were pretreated with 60 mg/kg morphine sulfate or 4 mg/kg ethanol i.p.; controls were left untreated. Four animals were used per group. Five minutes later, 30μC/kg C^{14}-labeled 5HTP were given i.p., and the animal was placed in the respirometer. The radioactive carbon dioxide level was recorded continuously in the expired air. A schematic diagram of the apparatus for decarboxylase assay is given. The results obtained indicate that at the dosage levels used, both morphine and ethanol significantly inhibited the enzymatic decarboxylation of 5HTP and, thereby, the synthesis of 5HT. These findings suggest a possible mechanism by which these drugs may influence the level of biogenic amines in the CNS and, consequently, behavior and emotional state.

State University of New York
Brooklyn, New York

1256 Weisbach, Jerry A., Burns, Cynthia, Macko, Edward, & Douglas, Bryce. **Studies in the synthesis and pharmacology of aporphines.** Journal of Medicinal Chemistry, 6(2):91-97, 1963.

Eleven aporphines were prepared for pharmacological testing. Several aporphine precursors were also tested. To determine dose range, graded doses of each compound were administered orally to mice, which were then observed for gross behavioral changes, pupillary alterations, reaction to thermal pain, lowering of rectal temperature, muscle tonus, and toxicity. Local anti-inflammatory activity was measured in rats, using three parameters: pain, skin temperature, and edema. In some rats, pleural volume studies were also carried out. Analgesic and antihistamine properties, local anesthetic action, and cardiovascular effects were also investigated. Antiemetic studies were carried out in dogs of known sensitivi-

ty to aporphine. All but one of the compounds screened in the mouse dose range produced CNS depression. Doses at or above the minimal required to elicit CNS depression were generally characterized by an increase in thermal pain threshold and by hypothermia. Ptosis and mydriasis occurred in some cases. The toxic doses in the series ranged from 200 to > 300 mg/kg. In the test for anti-inflammatory activity, toxic manifestations were sometimes evident in the rat at correspondingly lower doses than in the mouse. Very little analgetic activity was found in the series; only one compound had antipyretic activity without untoward side effects. All compounds tested had adrenolytic ability. Compounds showing preliminary activity were tested further. It is concluded that the compounds in this series are not clinically useful as therapeutic agents.

Smith Kline and French Laboratories
Philadelphia, Pennsylvania

1257 Lindner, A., Claasen, V., Hendriksen, Th. W. J., & Kralt, T. **Reserpine analogs; phenethylamine derivatives.** Journal of Medicinal Chemistry, 6(2):97-101, 1963.

The pharmacological properties of a large number of reserpine analogs containing phenethylamine moieties were investigated. The compounds studied showed several interesting properties, especially as depressants, antispasmodics, and adrenolytics. A number of compounds also had bronchodilator activity. The more active blood pressure-lowering substances were tertiary phenethylamine and β-hydroxyphenylisopropylamine derivatives. Departure from the phenethylamine structure led to diminished activity; the distance between the amino and hydroxyl groups was also a factor. The tertiary β-alkoxyphenylisopropylamine derivatives were active antispasmodics. The phenethylamine derivatives with a small substituent at the nitrogen atom possessed marked adrenolytic activity; piperidine and p-hydroxyphenylisopropylamine derivatives were active. Other structure-activity relationships are discussed.

University of Vienna
Vienna, Austria

1258 Sletzinger, M., Chemerda, J. M., & Bollinger, F. W. **Potent decarboxylase inhibitors. Analogs of methyldopa.** Journal of Medicinal Chemistry, 6(2):101-103, 1963.

Two classes of compounds analogous to α-methyldopa were prepared by substituting α-hydrazino or α-hydroxyl groups for the α-amino group of the parent compound. The compounds were then compared with α-methyldopa in their ability to inhibit mammalian DOPA-decarboxylase in vitro. Both classes of compounds were potent inhibitors; DL-α-hydrazino-α-(3,4-dihydroxybenzyl)propionic acid exhibited a potency about 1,000 times that of the parent compound.

Merck Sharp and Dohme Research Laboratories
Rahway, New Jersey

1259 Graham, J. D. P. & Karrar, M. A. **Structure-action relations in N,N-dimethyl-2-halogenophenethylamines.** Journal of Medicinal Chemistry, 6(2):103-107, 1963.

Antagonism to epinephrine, norepinephrine, and histamine was investigated in a series of 33 compounds related to N,N-dimethyl-2-halogenophenethylamine. Three groups of compounds were prepared: those with a ring substitution meta or para to the ethylamine side chain, those with ring substitutions meta and para to the side chain, and those with an ethanolamine side chain. All the compounds antagonized the spasmogenic action of histamine on isolated guinea-pig ileum. Antihistamine activity was increased by disubstitution in the ring. All the compounds except the ethanolamines antagonized the pressor response to epinephrine and norepinephrine. The most active antiepinephrine tested was the methyl-m-bromo compound. The relation between structure and antagonism is discussed in some detail.

Welsh National School of Medicine
Cardiff, Wales

1260 Thomas, J. & Marlow, W. **Quaternary ammonium compounds. III. Antiacetylcholinesterase activity and charge distribution in aromatic quaternary ammonium compounds.** Journal of Medicinal Chemistry, 6(2):107-111, 1963.

A series of trimethylphenylalkylammonium compounds were prepared and tested for anti-acetylcholinesterase activity. Results indicated that quaternary ammonium compounds in which the quaternized nitrogen atom is adjacent to an aromatic ring are more active than those in which the quaternary ammonium group is removed from the benzene ring and is of the aliphatic type. The results are discussed in terms of charge delocalization and stereochemistry of the two types of

quaternary ammonium ion.

University of Manchester
Manchester, England

1261 Reber, L. J., Allen, C. H., Durant, R. C., & Friess, S. L. **Structure vs. toxicity relationships in aryl esters of tropine and ψ-tropine. V.** Toxicology and Applied Pharmacology, 5:625-636, 1963.

Acute toxic effects of 2 new esters of ψ-tropine with methyl and methoxy-substituted phenylacetic acids were studied in the intact mouse and cat, and their potentiating and blocking effects on excised phrenic nerve--diaphragm (PND) preparations of the rat were investigated. The acute LD_{50} via i.v. was determined in 10 NMRI white mice (males, 18 to 22 g in weight), injected at closely spaced dose levels. Drug effects with the PND preparation were measured 3.0 minutes after addition of a drug to the bathing medium. The toxic effects of both compounds in mice and cats conform, in general, to the spectrum of toxic manifestations of most esters. Assigning the numerical values for the polar substituent constants σ^* to all esters of both amino alcohol series revealed a sharply descending linear relationship with the log LD_{50} scale, with the exception of those with negative or relatively small σ^*. This implies that the stereochemistry of the amino alcohol part of the ester is less important than the relative electronegativity of the aryl function. In general, the new esters follow the normal pattern of behavior in their effects on twitch response in the rat PND preparation via direct and indirect stimulation. This is exhibited in varying degrees of twitch amplitude potentiation at low concentration, followed by overriding twitch blockage at higher concentration. Curarization was found ineffective in altering the dose-response pattern on either the potentiation or blocking segments of the total curve for direct stimulation twitch.

Naval Medical Research Institute
Bethesda, Maryland

1262 Dudel, J., Gryder, R., Kaji, A., Kuffler, S. W., & Potter, D. D. **Gamma-aminobutyric acid and other blocking compounds in crustacea. I. Central nervous system.** Journal of Neurophysiology, 26(5): 721-728, 1963.

The constitutents of the CNS of lobsters (Homarus americanus) were surveyed, and blocking compounds were isolated and identified. A superficial fiber of the dissected opener muscle was impaled with a microelectrode, stimulated electrically, and the test compound was dropped onto the muscle. The CNS was dissected and placed on dry ice, lyophilized, and ground to dry powder, yielding 29.8 g from 500 1-pound lobsters. This was extracted with water, dialyzed, lyophilized, desalted with ion exchange resin, washed with NH_4OH, and lyophilized again. The NH_4OH eluate was separated into excitatory and blocking substances by chromatography. Chromatography and electrophoresis of the blocking substance yielded GABA, betaine, and taurine. Probably about 14% of the total activity was due to taurine, about 14% to betaine, and about 65% to GABA. The 29.8 g of powder contained about 16 mg GABA. The possibility that the active compound was β-hydroxy-GABA was excluded by chromatography. All these substances increased the ionic conductance of the muscle membrane, and therefore, at least a portion of their action was postsynaptic. The presence of the blocking compounds alanine and β-alanine was established by chromatography. These could not have accounted for more than about 5% of the total blocking activity in the extracts. Less than 5% of the blocking activity was also associated with an unidentified Sakaguchi- and Ninhydrin-positive compound. Glutamic acid, the major excitatory substance in the original extract, was identified by paper chromatography.

Harvard Medical School
Boston, Massachusetts

1263 Fotherby, K., Ashcroft, G. W., Affleck, J. W., & Forrest, A. D. **Studies on sodium transfer and 5-hydroxyindoles in depressive illness.** Journal of Neurology, Neurosurgery and Psychiatry, 26: 71-73, 1963.

This article investigates the claim that the rate of transfer of Na^{24} from blood to cerebrospinal fluid was lower in patients with a depressive illness than in schizophrenic patients, and that the rate returned to normal as the patients improved clinically. Data on the levels of 5-hydroxyindoles in blood and cerebrospinal fluid are also presented. Eleven depressives, 11 schizophrenics, and 6 exercized patients (either depressive or schizophrenic) were injected i.v. with 100μC Na^{24} in isotonic solution and, 30 minutes later, with 1/6 gr morphine and 1/100 gr hyoscine. One hour later, 10-ml cerebrospinal fluid was obtained by lumbar puncture and 2.5- and 10-ml samples of blood were taken. The results showed no significant difference between these two groups in the rate of transfer of Na^{24}. The transfer rate of a small group of depres-

sives who showed severe depression without paranoid symptoms was lower than that of the whole group of depressives. Exercise appeared to increase the transfer rate, which may have been caused by more rapid mixing of ventricular fluid with cerebrospinal fluid. There were no significant differences between the two groups in the levels of 5-hydroxyindoles in blood or in cerebrospinal fluid. The levels in cerebrospinal fluid tended to rise after exercise.

Postgraduate Medical School
Ducane Road, London, England

1264 Walaas, Eva, Walaas, Otto, Haavaldsen, Synnöve, & Pedersen, Björn. **Spectrophotometric and electron-spin resonance studies of complexes of catecholamines with Cu(II) ions and the interaction of ceruloplasmin with catecholamines.** Archives of Biochemistry and Biophysics, 100:97-109, 1963.

The complex formation of catecholamines with Cu(II) ions, and their interaction with the copper-containing enzyme ceruloplasmin, have been investigated, with special emphasis on complex formation in the absence of oxygen. In argon, stable 1:2 copper(II)ion-catecholamine complexes with definite optical properties have been observed. The electron-spin resonance (ESR) absorption spectra of these complexes in solution have been recorded. They exert the same characteristics as described for Cu(II) complexes with small molecules in general. Introduction of oxygen initiates the transformation of the catecholamines to the corresponding indolic structures, the adrenochrome, and the noradrenochrome, with characteristic optical properties. The ESR absorption spectra of the complexes are retained in the oxygen-containing solution, but the hyperfine structure is diminished. The effects of Cu(II), ethylenediaminetetraacetic acid and cyanide, and pH are also discussed. The interaction of catecholamines with ceruloplasmin in the absence of oxygen is characterized by the disappearance of the 605-mμ absorption band. At the same time, the ESR signal of ceruloplasmin completely disappears. Introduction of oxygen reactivates the enzyme and promotes oxidation of the ligand. Simultaneously, the ESR absorption spectrum of the enzyme partly reappears. A cupric-cuprous couple has been indicated for the mechanism of enzyme action. The mechanism of electron transfer during oxidation of catecholamines by the model complexes and by ceruloplasmin has been discussed.

University of Oslo
Oslo, Norway

1265 Nashold, Blaine S., Jr. & Kirshner, Norman. **The metabolism of adrenalin and noradrenalin in patients with basal ganglia disease.** Neurology, 13:753-757, 1963.

This study was done to determine: (1) whether patients with basal ganglia disease excreted significantly different amounts of catecholamines than normal patients; (2) whether surgical procedures altered the excretion; and (3) whether patients with parkinsonism metabolized an infused dose of noradrenaline-C^{14} in any manner different from normal patients. Two to three preoperative and three to four postoperative 24-hour urine specimens were collected from each patient. Patients with basal ganglia disease and those hospitalized for other causes (controls) were used. The catecholamines were assayed fluorometrically. Both groups of patients excreted normal amounts of adrenaline and noradrenaline. In the metabolism study, one group of six patients with parkinsonism and one patient with Huntington's chorea and another group of seven patients hospitalized for other causes were infused with 10μC of dl-noradrenaline-2-C^{14} in 500 ml physiological saline for 1 hour. Urine was collected at the end of infusion, at 1-hour intervals for 5 hours, and at 6-hour intervals for 18 hours. Total radioactivity was assayed by liquid-scintillation spectrometry, and the catecholamines were eluted and separated from each other by paper chromatography. The metabolism in both groups was found to be similar and comparable to that of a group of healthy young adults studied previously.

Duke University Medical Center
Durham, North Carolina

1266 de Jaramillo, Gabriella Anna V. & Guth, Paul S. **A study of the localization of phenothiazines in dog brain.** Biochemical Pharmacology, 12:525-532, 1963.

Chlorpromazine, prochlorperazine, and thiethylperazine were used to investigate CNS localization of phenothiazines. Young mongrel male dogs (10 to 14 kg in weight) were sacrificed 15, 30, 45, 60, and 90 minutes after injection of one of the phenothiazines. The drugs were always injected into the cephalic vein. The doses were 10 mg/kg and the volume injected never more than 6.0 ml. Chlorpromazine and prochlorperazine were injected in aqueous solution. Thielthylperazine was dissolved in a sodium bicarbonate--propylene glycol--water vehicle. After decapitation, the head was perfused through the carotid artery with 500 ml of 0.1 M phosphate buffer. The brains were removed

intact; the weights of each zone were recorded; and 1 g of each zone was taken for extraction. Fourteen regions of the brain were studied. Twenty-five to 50 of the extracts were spotted on Whatman #1 paper in parallel and were subjected to ascending chromatography. Development of chromatograms of these mixtures revealed only one spot. Recovery values with prochlorperazine and thiethylperazine were of the order of 95%; for chlorpromazine, the mean was 88%. Chlorpromazine and prochlorperazine exhibited similar spectra of localization in the 14 areas of dog brain surveyed. Thiethylperazine exhibited highest concentrations in the cerebellar areas.

Tulane University School of Medicine
New Orleans, Louisiana

1267 Evans, E. A., Eisenlord, G., & Hine, C. H. **Studies in detoxication by means of the isolated perfused liver.** Toxicology and Applied Pharmacology, 5:129-141, 1963.

The clearance rates of various doses of ethanol, pentobarbital, morphine, and lead were measured in the isolated perfused rat liver. Results with normal livers were compared with those from livers from animals damaged by 480 mg/kg of either carbon tetrachloride or allyl alcohol or by 0.5 ml of 5% sodium-potassium oxalate (pentobarbital). Livers from male rats of the Long--Evans strain (400 to 500 g in weight) were used for all perfusions. Smaller male and female rats of the same strain were used as blood donors. The perfusate (150-ml final volume, except for those containing lead, which was 180 ml) consisted of one part of heparinized whole rat blood diluted with two parts of albumin--Locke's solution. The rate of ethanol clearance was depressed in the allyl alcohol-damaged livers, and pentobarbital clearance was depressed in the oxalate-damaged livers. Lead clearance was increased in all damaged livers, but no significant differences were found in morphine clearance. Liver damage was assessed by measuring perfusate flow or bromosulfalein clearance bile production. This preparation offers the toxicologist an excellent method of measuring the hepatic metabolism or the hepatotoxicity of chemicals. It also has the advantage of preserving liver structure and function while removing the liver from the influence of other organs.

University of California
San Francisco, California

1268 Cignarella, Giorgio, Occelli, Emilio, Maffii, Giulio, & Testa, Emilio. **Bicyclic homologs of piperazine. Synthesis of pharmacologically active 8-methyl-3,8-diazabicyclo[3.2.1]octanes. III.** Journal of Medicinal Chemistry, 6(1):29-36, 1963.

A series of 3-alkyl-, 3-aralkyl-, and 3-acyl-substituted 8-methyl-3,8-diazabicyclo[3.2.1]octanes were synthesized for pharmacological screening. In mice, behavioral changes produced by these compounds were unspecific and were found only after the administration of nearly lethal doses. When given i.p. in doses as high as 10% of the LD_{50}, none of the compounds protected mice from the tonic phase of maximal electroshock seizures. No significant change in the pain threshold of rats was observed after i.p. treatment. None of the substances produced significant changes in the activity of carbonic anhydrase, acetylcholinesterase, pseudocholinesterase, or MAO. Several compounds had local anesthetic action, but only one was without any pharmacological side effects. Anticholinergic, spasmolytic, and antihistamine action were also apparent in the series. The tropoyl and dl-methyltropoyl derivatives were highly active in antagonizing the effect of acetylcholine. Four compounds had diuretic action.

Lepetit S.p.A.
Milan, Italy

1269 Drain, D. J., Howes, J. G. B., Lazare, R., Salaman, Ann M., Shadbolt, R., & Williams, H. W. R. **Monoamine oxidase inhibitors. The synthesis and evaluation of a series of substituted alkylhydrazines.** Journal of Medicinal Chemistry, 6(1):63-69, 1963.

Forty-two aryloxy-, arylthio-, and arylaminoalkylhydrazines were prepared and evaluated as in vitro and in vivo inhibitors of MAO. Of the compounds studied, 2-phenylthioethylhydrazine and (1-methyl-2-phenoxyethyl) hydrazine were the most active. Results of in vitro tests showed that the compounds were, in general, highly active inhibitors. When the effect of varying the length of the alkylene chain separating the phenoxy and hydrazine groups was studied, it was found that those compounds with two or four methylene groups were potent inhibitors, whereas those with three, five, or six had little activity. In general, only methoxy or methylene-dioxy substitutions on the phenyl ring yielded compounds of high potency.

Smith and Nephew Research Ltd.
Ware, Hertfordshire, England

1270 Whittaker, V. P., Michaelson, I. A., & Kirkland, R. J. **The separation of synaptic vesicles from disrupted nerve-ending particles.** Biochemical Pharmacology, 12:300-301, 1963.

Guinea-pig brain was homogenized in 0.32 M sucrose and subjected to differential and density gradient centrifugation to isolate a relatively pure fraction of nerve-ending particles torn away from their presynaptic and postsynaptic attachments. The P_2 fraction was uneserinized, suspended in water (2 ml/g original tissue), and centrifuged at 10,000 X g for 20 minutes. The supernatant fluid was subjected to density gradient centrifugation (7 gradients) at 53,500 X g for 2 hours. Assay showed that the second fraction (0.4 M sucrose) had the highest acetylcholine and specific activities, and electron microscopic examination showed it consisted almost entirely of synaptic vesicles. A second acetylcholine peak occurred in particulate layers of partially disrupted nerve-ending particles, lying between the sucrose layers of higher molarity. Brain lactic dehydrogenase, representing soluble cytoplasm released from disrupted nerve-ending particles, was recovered mainly from the supernatant layer. Finally, choline acetylase distribution resembled that of lactic dehydrogenase rather than that of acetylcholine, suggesting that acetylcholine is synthesized in the nerve-ending cytoplasm rather than in the synaptic vesicles.

A.R.C. Institute of Animal Physiology
Babraham, Cambridge, England

1271 Alleva, John J. **Metabolism of tranylcypromine-C^{14} and dl-amphetamine-C^{14} in the rat.** Journal of Medicinal Chemistry, 6(6):621-624, 1963.

The metabolism of tranylcypromine and amphetamine was studied, using the C^{14} form of each compound. Following single s.c. or oral doses of either drug, most of the administered C^{14} was recovered in the urine within 24 hours. However, small amounts of C^{14} were excreted in feces and urine for at least 4 days after s.c. injection. Expired carbon dioxide collected for periods of 4 and 6 hours after a single 5 mg/kg injection of tranylcypromine contained only traces of C^{14}. The amounts excreted in the urine during these periods were 16.3% and 42.9%, respectively. Urine chromatograms showed that, after a single 5 mg/kg dose of tranylcypromine-C^{14}, about 4% of the dose was excreted in the 24-hour urine as the parent compound and about 12% as hippuric acid-C^{14}. Corresponding values for dl-amphetamine-C^{14} were 15% and 2%. The identification of hippuric acid as a metabolite of tranylcypromine is evidence that cleavage of the cyclopropyl ring is a metabolic pathway.

Smith Kline and French Laboratories
Philadelphia, Pennsylvania

1272 Kravitz, E. A., Kuffler, S. W., Potter, D. D., & van Gelder, N. M. **Gamma-aminobutyric acid and other blocking compounds in crustacea. II. Peripheral nervous system.** Journal of Neurophysiology, 26(5):729-738, 1963.

A parallel survey was made of the blocking compounds in the peripheral nervous systems of the crab and lobster. Ten blocking agents were isolated. The GABA, taurine, and betaine contributed most of the blocking activity of the tissue extracts. Other compounds were β-alanine, alanine, homarine, glutamine, aspartic acid, and two unidentified substances. These materials were separated by electrophoretic and paper chromatographic techniques, and GABA was further identified by a specific enzymic assay procedure. The GABA had the strongest blocking activity. The only excitatory substance in the extracts was glutamic acid. It does not appear that GABA is produced by destruction of a larger molecule during extraction. The GABA content of peripheral nervous tissues increased together with the proportion of known inhibitory axons.

Harvard Medical School
Boston, Massachusetts

1273 David, J. P., Murayama, S., Machne, X., & Unna, K. R. **Evidence supporting cholinergic transmission at the lateral geniculate body of the cat.** International Journal of Neuropharmacology, 2(3-4):113-125, 1963.

The action of cholinergic drugs on the lateral geniculate body of the cat was studied. The following drugs were used: acetylcholine, arecoline, muscarine, acetyl-B-methacholine, physostigmine, atropine, dihydro-β-erythroidine (DHE), d-tubocurarine, epinephrine, and 5HT. The neurons in the dorsal nucleus of the lateral geniculate body in encéphale isolé preparations were activated by orthodromic stimulation of the contralateral optic nerve and by antidromic stimulation of the optic radiation. The effects of the drugs given by intracarotid injection were evaluated by noting the amplitude, latency, duration, and refractory period of the geniculate response. Post-tetanic potentiation was studied in control and drug-

treated preparations. The postsynaptic component was readily depressed by DHE, depressed to a lesser extent by atropine, and unaffected by d-tubocurarine; it was enhanced by low concentrations of acetylcholine and by physostigmine. Higher concentrations of acetylcholine had a depressant effect. Tetanic stimulation of the optic nerve relieved the depression imposed by DHE and by atropine. It depressed the postsynaptic wave after the wave had been enhanced by low doses of acetylcholine. The presynaptic spike, the antidromic response, and the refractory period remained unaltered after drug administration. The 5HT produced a depression of the postsynaptic component, which was not relieved by tetanic stimulation. The data evidenced a close resemblance between the pharmacological responses of Renshaw cells and of geniculate neurons, and indicate that at least one of the mechanisms subserving transmission in the lateral geniculate nucleus is cholinergic in nature.

University of Illinois
Chicago, Illinois

1274 Brzezinski, A., Koren, Z., Pfeifer, Y., & Sulman, F. G. **The metabolism of serotonin in amniotic fluid.** Journal of Obstetrics and Gynaecology of the British Commonwealth, 69(4):661-664, 1962.

To test the hypothesis that the amniotic fluid lacks serotonin because serotonin is rapidly metabolized within the fluid by MAO or other enzymes, the breakdown of 5HIAA—the main metabolite of serotonin—and serotonin was tested in 40 specimens of amniotic fluid and urine. Serotonin breaks down in the amniotic fluid, but not in the urine. Circumstantial evidence of the existence of MAO in amniotic fluid and its kinetics in serotonin metabolism is presented. The effect of serotonin decomposition in the amniotic fluid on fetal life is discussed.

Rothschild-Hadassah University Hospital
Jerusalem, Israel

1275 Gothelf, Bernard & Karczmar, Alexander G. **Distribution of intravenously administered chlorpromazine in cat tissues.** International Journal of Neuropharmacology, 2(1-2):39-49, 1963.

Tissue distribution of chlorpromazine was measured in cats for 48 hours after drug administration; certain behavioral and pharmacological observations were correlated with tissue levels of chlorpromazine. Doses of 40μg/g (30 cats) and 20μg/g (2 cats) were given i.v. into the saphenous or femoral vein. Immediately following the administration of chlorpromazine, levels near 1 mg/g could be determined in the heart and in the lung. Altogether, there was a rapid shift of chlorpromazine from the blood to other tissues. At 1 hour, chlorpromazine concentrated 4- or 5-fold in the lung, liver, and brain; chlorpromazine content of the heart and other tissues was relatively low. For 12 hours after its administration, chlorpromazine content remained high in the liver; it decreased abruptly between 12 and 24 hours. The lung level of chlorpromazine remained at a high level even 48 hours after its administration; brain levels decreased slowly from the 1-hour peak. While, at various times, the cerebrum, brain stem, and hippocampus exhibited particularly high levels of chlorpormazine compared to other brain areas, these differences never exceeded 50% and were generally less marked. Pharmacological actions of chlorpromazine did not terminate simultaneously. Hypothermia and analgesia seemed to be associated with the 30μg/g to 50μg/g chlorpromazine levels in various parts of the brain; tranquilization appeared to require less chlorpromazine.

Veterans Administration Hospital
Hines, Illinois

1276 Firemark, H., Barlow, C. F., & Roth, L. J. **The entry, accumulation and binding of diphenylhydantoin-2-C^{14} in brain. Studies on adult, immature and hypercapnic cats.** International Journal of Neuropharmacology, 2(1-2):25-38, 1963.

The penetration of diphenylhydantoin into cat brain, using the techniques of radioassay and autoradiography, the role of tissue binding in influencing diphenylhydantoin accumulation in mature and immature cat brain, and the effect of hypercapnia on the penetration of diphenylhydantoin into the CNS were investigated. Diphenylhydantoin penetrates the brain rapidly, and concentrations two-to-three-fold greater than plasma levels are found in all brain regions for 24 hours after injection. Diphenylhydantoin is found in brain and plasma. The drug concentration in cerebrospinal fluid is equivalent to the concentration in ultrafiltrates of brain and plasma. The early pattern of brain penetration is limited by circulation, as indicated by the high concentrations in brain regions with high blood flow and vascularity. Hypercapnia does not alter the concentration

of diphenylhydantoin in brain. Drug concentration is lower in newborn brain, but increases with maturation and the increase in brain solids. The drug accumulation per dry weight of brain solid is higher in gray matter than white matter, suggesting that the binding of diphenylhydantoin in brain may be an interaction with nonlipid brain constituents.

The University of Chicago
Chicago, Illinois

1277 Sveshnikova, N. A. **Hexokinase activity of homogenates of brain and cardiac and striated muscle of narcotized animals.** Bulletin of Experimental Biology and Medicine, 56(8):880-882, 1963.

Because not enough is known about the enzyme systems concerned with glycolysis under narcosis, hexokinase activity was assessed in homogenates of various tissues by the method of Long. The test animals were rats. Four series of experiments with brain and myocardial tissues were performed: (1) Animals were not anesthetized (controls). (2) Animals were subjected to deep ether narcosis of short duration (15 to 30 minutes). (3) Animals were subjected to light ether narcosis of long duration (90 to 120 minutes). (4) Animals were made unconscious by an s.c. injection of 1.2 to 2 ml of 4% pentothal. The hexokinase activity of striated muscle was determined at the beginning and at the end of narcotization, because this tissue has a relatively low hexokinase activity and a high glycogen content. These experiments have given no indication of any fall in hexokinase activity in the brain, the myocardium, or the striated muscle of rats under ether or pentothal narcosis. In some cases, an increase in activity was observed in heart muscle. In conclusion, the reduced carbohydrate metabolism of anesthetized animal tissues cannot be due to interference with the enzyme reaction, but it may be due to lowered permeability of the cells to glucose.

S.M. Kirov Leningrad Order of
Lenin Institute for Post-Graduate Training
of Physicians
Leningrad, U.S.S.R.

1278 Sunshine, Irving. **Use of thin layer chromatography in the diagnosis of poisoning.** American Journal of Clinical Pathology, 40(6):576-582, 1963.

Comprehensive data are given on the application of thin-layer chromatography on silica gel G covered glass plates to several categories of drugs in general use and to their detection in blood, urine, stomach contents, and tissues. Identification is simplified by calculating the ratio of the R_f of the sample to the R_f of a known "marker" compound. The technique compensates for any variation in conditions that tend to make R_f values variable. Results for barbituric acids with phenobarbital as marker, phenothiazines and organic bases with propiomazine as marker, and tranquilizers with meprobamate as marker are tabulated. The total time required for a rapid scan of biological fluids is about 3 hours.

Western Reserve University School of Medicine
Cleveland, Ohio

1279 Eagleson, D. Alan. **Paper chromatographic differentiation of some important phenothiazines encountered in toxicology.** American Journal of Clinical Pathology, 39(6):648-651, 1963.

A method is described for the chromatographic differentiation and identification of phenothiazine derivatives by measuring R_f values. Three solvent systems were used: butanol-HCl--water; butanol--acetic acid--water; and isobutyl alcohol--propionic acid--water. The R_f values for chlorpromazine, promazine, triflupromazine, prochlorperazine, trifluoperazine, thiopropazate, mepazine, and perphenazine in each of the three solvent systems are tabulated.

Tacoma General Hospital
Tacoma, Washington

1280 Adler, Terrine K. & Albert, Adrien. **The biological and physical properties of the azaindoles.** Journal of Medicinal Chemistry, 6(5):480-483, 1963.

The acute pharmacological effects of monoazaindoles and polyazaindoles in mice and their in vitro effects on smooth muscle were investigated. Some physical properties of the compounds were also studied. Among the monoazaindoles, only the 4-isomer resembled indole in producing depression of smooth muscle as well as stimulation of the CNS. The other monoazaindoles share either one or the other of these properties: 3-aza- and 7-azaindole produced depression of both systems; and 5-aza and 6-azaindole produced stimulation. Depression of smooth muscle occurred with 2-azaindole, but it produced

mixed stimulant and depressant effects in the CNS. Small doses of 2,3-diazaindole (benztriazole) and 3,5-diazaindole resulted in mixed effects, appearing as occasional clonic seizures superimposed on a flaccid paralysis. The physical properties of the azaindoles are not well correlated with biological action, although they are well correlated with structure; the position of the doubly-bonded nitrogen appears to be a significant factor.

University of California Medical Center
San Francisco, California

1281 Holland, Gerald F., Funderburk, William H., & Finger, Kenneth F. **Preparation and anticonvulsant activity of N-substituted benzenedisulfonamides.** Journal of Medicinal Chemistry, 6(3):307-312, 1963.

A series of N-substituted 3- and 4-benzenedisulfonamides were synthesized and screened in male mice to determine their ability to protect against electroshock convulsions. The 4-benzenedisulfonamides were the more potent anticonvulsants. In this series, substituents which were lipophilic in nature (such as alkyl, haloalkyl, aryl, and aralkyl) had a favorable effect on anticonvulsant activity. Increasing the size of the lipophilic substituent decreased activity. Some of the compounds tested were more active than acetazolamide or ethoxzolamide. The potent anticonvulsant and in vivo carbonic anhydrase inhibitory activity of N-isopropyl-4-benzenedisulfonamide suggests, for the N-substituted compounds in general, a correlation between the two pharmacological effects.

Charles Pfizer and Company, Inc.
Groton, Connecticut

1282 Belleau, B. & Puranen, J. **Stereochemistry of the interaction of enantiometic 1,3-dioxolane analogs of muscarone with cholinergic receptors.** Journal of Medicinal Chemistry, 6(3):325-328, 1963.

The synthesis of L(+)-cis-2-methyl-4-trimethylammoniummethyl-1,3-dioxolane iodide (I) and its enantiomer (II) are described. The cholinomimetic activity of I was found to be 100 times that of II and 6 times that of acetylcholine.

University of Ottawa
Ottawa, Canada

1283 Loomis, T. A. **Distribution and excretion of pyridine-2-aldoxime methiodide (PAM); atropine and PAM in sarin poisoning.** Toxicology and Applied Pharmacology, 5:489-499, 1963.

The distribution and excretion of pyridine-2-aldoxime methiodide (PAM)-C^{14} in mice and dogs after poisoning with sarin was studied to obtain information regarding the failure of PAM to be an effective antidote in anticholinesterase poisoning in the absence of atropine. After i.v. injection, PAM penetrates readily into the liver and kidney of mice and into most soft tissues of the dog. No isotope was found in the brain of the mice, and only trace amounts of isotope were found in the brain of one dog. Isotope is retained in the tissues except for brain after it has been cleared from the blood. Approximately 50% of the isotope was recovered in the urine in 90 minutes. In a single human being, 65% of i.v. injected isotope was recovered in 2 hours. Spontaneous motor activity of mice is decreased following small doses of sarin. This effect of sarin is antagonized by atropine but not by methylatropine or PAM. The mortality in mice injected i.p. with 2 LD50's of sarin was not influenced by prophylactic i.p. injection of atropine, methylatropine, PAM, or methylatropine plus PAM. Atropine plus PAM produced complete protection against the above dose of sarin. The effect of atropine when used in combined atropine--oxime therapy of anticholinesterase poisoning is ascribed to its ability to protect the CNS from effects of the antiesterase.

University of Washington
School of Medicine
Seattle 5, Washington

1284 Barbeau, André, Jasmin, Gaétan, & Duchastel, Yves. **Biochemistry of Parkinson's disease.** Neurology, 13:56-58, 1963.

Serum magnesium and 5HIAA determinations were run in normal and parkinsonian subjects to elucidate possible abnormal metabolism in Parkinson's disease. Urinary excretion of 5HIAA, a metabolite of serotonin, was measured in 27 parkinsonian subjects and in 56 normal subjects. This excretion was significantly decreased in parkinsonian patients, suggesting a defect in the tryptophan metabolic pathway similar to the previously demonstrated defect in the phenylalanine pathway. Serum magnesium levels in 28 parkinsonian subjects were significantly decreased compared to levels in 20 nonparkinsonian subjects. The correlation be-

tween these two findings is discussed in relation to the etiology of some of the symptoms of Parkinson's disease.

Université de Montréal
Montréal, Quebec, Canada

1285 Sunshine, Irving, Rose, Eleanor, & Le Beau, Jack. **Barbiturate detection using thin-layer chromatography.** Clinical Chemistry, 9(3):312-316, 1963.

Thin-layer chromatography is suggested as a new technique that will permit the average laboratory to analyze, with relative ease and economy, biologic materials for the presence of barbiturates. Twenty-three standard barbiturate acids (10 mg/100 ml in chloroform) were identified, using standard thin-layer chromatography techniques. The R_f ratios of barbiturate acids to that of simultaneously run phenobarbital are given. In addition to pure drugs, this method has been successfully applied to biologic samples from over 100 victims of barbiturate intoxication. In 90 to 120 minutes, a report could be made as to whether or not one or more barbiturates were present and which drugs were probably implicated, as well as an educated guess as to the amount present. It has an advantage over spectrophotometry in that one can ascertain whether more than one barbiturate is involved. Unfortunately, the method is not quantitative.

Western Reserve University
Cleveland 6, Ohio

1286 Beckett, A. H., Beaven, M. A., & Robinson, Ann E. **Metabolism of chlorpromazine in humans.** Biochemical Pharmacology, 12:779-794, 1963.

Isolation of some of the glucuronic acid conjugates formed by the metabolism in vivo of chlorpromazine and promazine, and characterization of some other metabolites of chlorpromazine present in the urine of psychiatric patients are reported. Twenty-four-hour urine samples were collected from male patients receiving 150 to 600 mg/day chlorpromazine hydrochloride p.o. Patients previously untreated with phenothiazines provided control specimens and 48-hour specimens after a single p.o. dose of 100 mg chlorpromazine hydrochloride. Paper chromatographic and electrophoretic methods are described; assay methods for glucuronic acid and "phenothiazine equivalencies" of metabolit fractions (for cases where no suitable reference compound was available) are given. Methods for quantitative estimation of total phenothiazine content, free chlorpromazine metabolite content, and chlorpromazine glucuronide content in urine are given. Methods for enzymic hydrolyses with β-glucuronidase and aryl sulfatase are described. It is shown that chlorpromazine and its mono- and di-demethylated derivatives are hydroxylated, and that these hydroxy compounds are conjugated mainly with glucuronic acid and, to a lesser extent, with sulfate. The predominant metabolite was isolated and identified as a monoglucuronide of N-desdimethyl chlorpromazine.

Chelsea College of Science and Technology
London, SW. 3, England

1287 Miyazaki, Yukio, Godaishi, Kotaro, Ogawa, Hideko, & Ito, Hiroshi. **The effect of the soil moisture upon the growth, yield, and alkaloid content of Rauwolfia serpentina Benth.** Bulletin of National Institute of Hygienic Sciences, 90:146-149, 1962.

The effects of soil moisture on the growth, yield, and alkaloid content of Rauwolfia serpentina was studied in potted plants with soil moisture content 100%, 80%, 60%, 40%, and 25% of the water capacity of the soil. The 100%, and especially the 80%, moisture-content plots showed the best plant top growth. Top growth was considerably inferior in the 60% and 40% plots, and reduction of growth was conspicuous in the 25% plot. Air-dried root weight was highest in the 80% plot, followed by the 60%, 100%, 40%, and 25% moisture-content plots. Soil moisture generally had little influence on total alkaloid content of the air-dried roots, although the 25% plot showed a slightly higher total alkaloid content. Difference in soil moisture content also seemed to have little effect on the reserpine--rescinnamine content of the roots.

(No address)

1288 Kawatani, Toyohiko & Ohno, Tadaro. **On the trial cultivation of Rauwolfias at Kasukabe, especially R. serpentina Benth. VI. Cultural condition of R. serpentina.** Bulletin of National Institute of Hygienic Sciences, 90:141-145, 1962.

Growth experiments were conducted on the effects of fertilizer containing three essential nutrients (nitrogen, phosphorus, and potassium), soil pH, and soil class on

the cultivation of Rauwolfia serpentina. Results showed that the three essential nutrients had no significant effect on growth of plant tops and weight of roots; growth is impossible at soil pH 3.0 and 3.5; soil pH below 4.5 and above 7.0 is not suitable from the standpoints of growth and root yield; suitable soil reaction seems to lie in the range from pH 6.0 to 6.5; volcanic ash loam, light clayey loam, and humus soil are suitable for cultivation of Rauwolfia serpentina from the standpoints of growth, root yield, and alkaloid content; sandy soil is not suitable.

(No address)

1289 Kveder, S., Iskrić, Sonja, & Keglević, Dina. **5-Hydroxytryptophol: A metabolite of 5-hydroxytryptamine in rats.** Biochemical Journal, 85:447-449, 1962.

The possibility of formation of an intermediate alcohol in the metabolism of 5-hydroxytryptamine was investigated. Adult male albino rats were given 2.9 mg/100 g 5-hydroxy[1'-C^{14}]tryptamine creatinine sulfate i.p. Urine (24-hour sample) was filtered through deactivated charcoal, and the phenolic eluate subjected to paper chromatography. The peak at R_f 0.46 yielded metabolite C, which was used throughout. Upon incubation with an excess of β-glucuronidase and addition of ethanol, metabolite C almost vanished and a new chromatographic spot, aglycone C, appeared. Chromatography of the liver reaction mixtures showed that 80% to 90% of N-acetyl-5-hydroxytryptamine had remained unchanged, but 60% to 70% of 5-hydroxytryptophol was metabolized. Because the chromatograms of metabolite C could indicate a glucuronide of either N-acetyl-5-hydroxytryptamine or 5-hydroxytryptophol, the isotope trapping technique was employed to identify the aglycone. Scanning records of the chromatograms of both the liver-reaction mixture and 24-hour urine sample showed radioactivity associated with the unmetabolized alcohol, but not with the N-acetyl compound. It is clear that radioactivity coincided with metabolite C only when 5-hydroxytryptophol was administered. Therefore, metabolite C is identified as a 5-hydroxytryptophol O-glucuronide and as a major metabolite of 5-hydroxytryptamine.

Institute Rudjer Bošković
Zagreb, Yugoslavia

1290 Posner, Herbert S. & Levine, Jerome. **Inability to validate the urinary FPN test for phenothiazine drugs: Suggestions as to the cause of the discrepancy.** Journal of Nervous and Mental Disease, 136(6):591-593, 1963.

The validity of the FPN-Universal Test for detecting phenothiazines in urine at high and low dosages was tested. Four series of tests were conducted. In each series, the test was rated by two people. It was concluded that the FPN test did not give valid results at doses below 70 mg/day, the range over which the low-dose drugs are generally given. Contrary to previous findings, treatment with Dowex AG 3X4, rather than improving the test, eliminated almost all color formation. Three factors contribute to the discrepancies produced by the test: (1) large degrees of rater variability in the low-dose (0 to 1+) range; (2) differences between patients with respect to absorption, metabolism, and/or excretion of the phenothiazine drugs; (3) magnification of individual variability because the test is utilized on low-dose drugs on an all-or-nothing basis (0 to 1+).

St. Elizabeths Hospital
Washington 20, D.C.

1291 Callingham, B. A. & Cass, Rosemary. **A modification of the butanol extraction method for the fluorimetric assay of catecholamines in biological materials.** (Letter) Journal of Pharmacy and Pharmacology, 15:699-700, 1963.

A modification of the Shore and Olin method for the extraction of catecholamines from tissues is presented, in which the tissue to be extracted is frozen in liquid nitrogen and crushed rather than homogenized. After immersion in liquid nitrogen, the tissue is dropped whole into a suitably sized stainless-steel-tablet die. The frozen tissue is crushed by striking the punch with a hammer, and the entire compressed pellet of still-frozen tissue is dropped into the Shore and Olin salt-saturated butanol. Hydrochloric acid (0.01 N) sufficient to produce a total aqueous phase of about one-tenth of the volume of butanol is added, together with 10 mg of sodium metabisulphite to reduce oxidation during extraction. The remainder of the assay procedure is like that of Cass and Spriggs. Results are given comparing noradrenaline contents of heart and brain measured with acid homogenization and with nitrogen

freezing. In both tissues, nitrogen freezing gave significantly higher values. Nitrogen freezing eliminates the frothing of the extracts and the overheating of the homogenizer.

School of Pharmacy
London, W.C.1, England

1292 Wollemann, Maria. **In vitro oxidation of DPNH by free radicals of chlorpromazine.** Biochemical Pharmacology, 12:757-768, 1963.

When chlorpromazine was partially oxidized with ceric sulfate and an equivalent amount of reduced diphosphopyridine nucleotide (DPNH), reduced triphosphopyridine nucleotide (TPNH), or sodium hydrosulfite was added, the wine-red color of the free radical disappeared. After a 10 mg/ml chlorpromazine solution was irradiated with a quartz lamp for 32 hours, a brownish-red color appeared which, after the addition of the same reducing agent, turned yellow. The absorption maximum of DPNH was studied at 340 mμ; its value decreased after the addition of irradiated chlorpromazine but not after chlorpromazine. The ultraviolet absorption spectrum of the free radical produced with ceric sulfate decreased after the addition of DPNH or TPNH. After the addition of DPNH or TPNH and extraction by the method of Salzman and Brodie, the free radical was found to be a mixture of chlorpromazine and chlorpromazine sulfoxide. When the extraction was repeated with the free radical alone, the appearance of chlorpromazine and chlorpromazine sulfoxide was also observed. When chlorpromazine was irradiated in the presence of 0.02 M ethylenediaminetetracetic acid (EDTA), the change in color stopped at the occurrence of a blue precipitate. It is suggested that some metal traces have a catalytic role in the oxidation reaction.

Institute of Neurosurgery
Budapest, Hungary

1293 Weiss, Benjamin & Rossi, G. **Metabolism of DOPA-^{14}C in the normal and α-methyldopa-treated mouse.** Biochemical Pharmacology, 12:1399-1405, 1963.

The disposition of exogenous DOPA in the intact mouse was studied, and an attempt was made to determine the DOPA-decarboxylase inhibitory activity of α-methyldopa in vivo. Swiss--Webster male mice (20 to 25 g in weight) were injected i.p. with 1μc DOPA-C^{14}. The DOPA-C^{14} was rapidly metabolized in the intact mouse; the biological half-life was approximately 15 minutes. Decarboxylation was an important, but not the only, route of metabolism. One hour after administration of DOPA-C^{14}, the following labeled catechols were found in whole-mouse homogenates (concentrations expressed as percent of total recovered radioactivity): DOPA (17.3%), dopamine (13.8%), norepinephrine (1.2%), epinephrine (0.5%), and dopac (0.8%). Doses of 3.12 mg/kg α-methyldopa i.p. inhibited the in vivo decarboxylation of DOPA-C^{14}. Larger doses of methyldopa produced greater inhibition; maximal response was obtained with 50 mg/kg. In mice given α-methyldopa (25 mg/kg) 30 minutes prior to DOPA-C^{14} and sacrificed 1 hour later, the DOPA level was increased (30.6%) and the dopamine level was reduced (3.8%). The in vivo duration of the decarboxylase inhibitory activity of α-methyldopa in the mouse was 8 to 16 hours.

Philadelphia College of Pharmacy and Science
Philadelphia, Pennsylvania

1294 Bhagat, B. **The role of adrenal medulla in maintenance of cardiac catecholamine levels in the rat.** (Letter) Journal of Pharmacy and Pharmacology, 15:847-848, 1963.

Male Holtzman rats (200 to 225 g in weight) were either demedullated or sham operated. Ninety-six hours after the operation, the rats were given Win 18501-2 (1-(5,6-dimethoxy-2-methyl-3-indole)-ethyl-4-phenylpiperazine), 50 mg/kg i.p., and were sacrificed at various times thereafter. The concentrations of catecholamines in the ventricular myocardium were determined by the trihydroxyindole fluorimetric method of Shore and Olin. The results showed that noradrenaline returned to control value in the sham operated rats within 18 hours after Win 18501-2. Demedullation significantly retarded the restoration of cardiac catecholamine after Win 18501-2, but it had no effect on normal levels of catecholamines on the heart. There was no significant difference in myocardial catecholamine levels between sham operated and demedullated rats.

University of Minnesota
Minneapolis, Minnesota

1295 Layne, D. S., Arai, Golab, K., & Pincus, G. **The metabolic fate of orally administered ^{3}H-norethynodrel and ^{3}H-norethindrone in humans.** Biochemical Pharmacology, 12:905-911, 1963.

Excretion of radioactivity in five women receiving tritiated norethynodrel and two women receiving tritiated norethindrone was measured to determine the metabolic fate of the two steroids. The subjects, ranging in age from 29 to 67, were psychiatric inpatients. Norethynodrel was given orally in doses of 5 mg/day to one patient and 10 mg/day to two patients on 1 day only; two patients were given 100 mg/day of nonradioactive norethynodrel for 7 days. Norethindrone was given orally to one patient at 10 mg/day and i.v. to one patient at 0.7 mg/day for 1 day. The steroids were given at 9 A.M., and urine collection was begun immediately thereafter. In four women, 38% of the orally administered H^3-norethynodrel was excreted in the urine. The two women receiving H^3-norethindrone excreted 70% and 50%, respectively, in their urine. Thirty percent of the dose of H^3-norethynodrel was found in bile collected from one subject. Thirty to sixty percent of both steroids were conjugated as glucosiduronate, and another 9% to 25% was presumed to be a sulfate conjugate. Conversion products of norethynodrel in the glucosiduronate fraction of the urine of two women were studied. They were mainly steroid alcohols, all but one of which had the ethynyl side chain. Only traces of ketosteroids were present, and no evidence was found of major conversion of norethynodrel to phenolic compounds.

The Worcester Foundation for Experimental Biology
Shrewsbury, Massachusetts

1296 McGeer, P. L., McGeer, E. G., & Boulding, J. E. **Excretion of 4-amino-5-imidazolecarboxamide by mental patients.** Archives of General Psychiatry, 8: 418-422, 1963.

Twenty-four hour urine specimens were obtained from 100 mental patients of both sexes (16 to 66 years of age), 32 of whom were not receiving drugs. The study continued for about 9 months, during which time urine samples were also collected from normal human beings and from general hospital patients. Diagnoses of and other data on the mental patients were obtained after the analyses had been completed. Creatinine was measured by Taussky's modification of Jaffe's reaction and 4-amino-5-imidazolecarboxamide (AIC) was determined by the method of McGeer et al. Creatinine was used as a reference standard and as a measure of the completeness of the 24-hour collections. The mean excretion levels of AIC or of creatinine by the groups of mental patients were not significantly different from the means for similarly aged groups of healthy individuals. There was no consistent difference in excretion levels between persons with schizophrenia and those with other forms of mental illness. Phenothiazine derivatives did not affect AIC excretion. There was a greater variability of AIC excretion in mental patients in comparison with normals.

University of British Columbia
Vancouver, British Columbia, Canada

1297 Rieder, J. & Roth, M. **A method for the determination of microquantities of iproniazid and other N_1-alkyl-N_2-acyl-hydrazines in body fluids and tissues.** Biochemical Pharmacology, 12:445-450, 1963.

In the quantitative method described, samples of body fluids or extracts of tissue homogenates in a buffer of pH 3.0 are saturated with sodium sulfate and magnesium oxide and then extracted by shaking with butyl-acetate-butanol. An aliquot of the organic extract is treated with a solution of blue tetrazolium and potassium hydroxide in methanol under standardized heating conditions. The tetrazolium salt is reduced by the hydrazine moiety of the drug with formation of the purple-colored formazan, the concentration of which is determined by spectrophotometry. The preparation of biological samples and the estimation of the drugs in body fluids and in tissues are fully described. The method of constructing a calibration curve and calculating results is given. The minimal concentration of iproniazid, isocarboxazid, or pivaloyl-benzylhydrazid that can be measured is 1μg/ml or 1μg/g of biological material. Reproducibility is excellent, and the method is sufficiently specific for the unchanged drugs.

F. Hoffmann-LaRoche and Co., Ltd.
Basle, Switzerland

1298 Williams, Clara H. & Livingston, Andrew. **Increased excretion of histidine found in paper chromatographic survey of dog urines.** Journal of Nervous and Mental Disease, 137(4):395-399, 1963.

Using bidimensional paper chromatography, a qualitative study of the fluorescent, phenolic, and indolic metabolites in the urine of 19 mixed-breed dogs was carried out. After urine samples were concentrated, 10λ amounts of the concentrate were spotted on Whatman #1 filter paper. Propanol--ammonium hydroxide--water (4:1:1) was the solvent system in the first dimension; butanol--glacial acetic acid--water (4:1:1) was used in the second dimension. The papers were air-dried for 24 hours before examination under ultraviolet light. One paper was sprayed with diazotized sulfanilic acid to detect phenolic compounds, and a second paper was sprayed with Ehrlich's reagent to detect indolic compounds. Histidine and imidazole were measured by the method of Cain and Berry. Chromatography revealed 29 spots with a frequency of occurrence from 14 to 100 percent. Seventeen spots were fluorescent, nine were diazo-coupling, and three were indolic. Eighteen of these spots have been found in human urines. Except in two dogs, the pattern of urinary metabolites was independent of the type of dog or of the urinary creatine content. Two dogs with "abnormal" conditional reflex behavior had a high urinary histidine content. Loading, in one of these dogs and in two normal dogs, produced no changes. Similar loading experiment with imidazole produced no behavioral changes.

Veterans Administration Hospital
Perry Point, Maryland

1299 Palmer, J. F. **The use of β-thiopropionic acid for stabilising the fluorescence of adrenolutine and noradrenolutine.** (Letter) Journal of Pharmacy and Pharmacology, 15:777-778, 1963.

A method is given for stabilizing fluorescence with β-thiopropionic acid (TPA) in the determination of adrenaline and noradrenaline (in nanogram quantities) by the fluorimetric trihydroxyindole method. The TPA effectively reduces the increase in fluorescence of both alkali--ascorbic and plasma--alkali mixtures. Results using TPA show a reproducibility of ±100 picrograms for adrenaline and noradrenaline. The improvement in the stability of the fluorescence is most useful at 436 mμ, although the parallel improvement at 405 mμ makes this latter wavelength most suitable for estimating small amounts of total adrenaline plus noradrenaline.

University of the West Indies
Jamaica, British West Indies

1300 Bhatt, K. G. S. & Sanyal, R. K. **Association of histamine and 5-hydroxytryptamine with the inflammatory processes.** (Letter) Journal of Pharmacy and Pharmacology, 15:78-79, 1963.

Histamine and 5HT levels were measured in rats after the production of aseptic inflammation. The affect of previous depletion of either amine on the production of inflammatory exudate or development of fibrous tissue was also studied. Control animals and those subjected to surgical trauma were sacrificed at intervals from 1 to 26 days after the operation. Extraction and assay for histamine and 5HT were according to the method of Parratt and West. Histamine values were reduced 25% in the first 24 hours. There was a return to control level by the fourth day, then a rise to 170% by the twelfth day before the final return to control level between days 16 to 26. The 5HT values showed a progressive rise from the beginning, reaching a maximum of 300% by the end of 1 week and returning to control level by the sixteenth day. In the adjacent and distal skin areas, values for both histamine and 5HT reached a maximum of 200% to 300% in 6 to 8 days and returned to control level in 16 to 26 days. Results from mice were similar. The exudative phenomenon was studied by the granuloma-pouch method and the development of fibrous tissue by the cotton-wool-pellet method. Results showed that the amount of exudate in the pouch was greatest in the control animals; in histamine-depleted animals, the values were about 35% of control, whereas values of 20% of control were obtained in animals depleted of 5HT. The latter group showed least inflammation. The maximum reduction in the development of fibrous tissue was in reserpine-treated animals.

Maulana Azad Medical College
New Delhi, India

1301 Bernsohn, Joseph, Barron, Kevin D., & Hedrick, Marjorie T. **Some properties of isozymes of brain acetylcholinesterase.** Biochemical Pharmacology, 12:761-763, 1963.

The properties of acetylcholinesterase isoenzymes were studed after separation by starch-gel electrophoresis. The two fastest-moving isoenzymes were, of necessity, treated as one band. The starch gel was homogenized with an equal volume of distilled water to which 2% gum acacia was added to stabilize the enzyme. This was dialyzed overnight against isotonic saline. Aliquots of the slurry were used as the enzyme source, and acetylcholinesterase activity was determined by a microtitrimetric method (Glick) using acetylcholine iodide as a substrate. The Km values were obtained by treatment of the data according to Lineweaver and Burk. The two acetycholinesterase isoenzymes described did not differ in pH optimum, substrate optimum, Km values, or pI_{50} values for eserine, Mytelase (N',N'-bis(2-diethylaminoethyl)oxamide bis-2-chlorobenyl chloride), or diisopropyl fluorophosphate (DFP).

Veterans Administration Hospital
Hines, Illinois

1302 Beckett, A. H. & Curry, S. H. **Spectroscopic studies of the reaction of hydroxylated promazines and related compounds with sulphuric acid.** Journal of Pharmacy and Pharmacology, 15(Supplement): 246T-252T, 1963.

To identify a promazine glucuronide of unknown structure, the differences in spectral characteristics of various hydroxyphenothiazines after treatment with sulfuric acid were studied; it was found that sufficient differences exist between the spectra produced by reference compounds to enable the position of ring hydroxylation of promazine metabolites to be determined. Spectra were run on the following reference compounds: 1-hydroxypromazine, 2-hydroxypromazine, 2-methoxypromazine, 2-methoxyphenothiazine, 3-methoxypromazine, 3-hydroxyphenothiazine, and 4-hydroxypromazine. Each compound (approximately 100µg) was dissolved in 70% ethanol, then added to equal parts of concentrated sulfuric acid and 70% ethanol. Absorption maxima for the reference compounds were determined between 200 to 700 mµ and tabulated. A careful comparison of the spectrum of the unknown aglycone after sulfuric acid treatment with the reference spectra provides evidence about the position of mono-hydroxylation of the promazine metabolite; it seems probable that monoglucuronides of promazine would have the same spectra as their aglycones. The nature of phenothiazine reaction products is discussed.

Chelsea College of Science and Technology
London, S.W.3, England

1303 Roberts, D. J. **Some factors affecting the R_f values of sympathomimetic catecholamines.** Journal of Pharmacy and Pharmacology, 15:532-537, 1963.

The behavior of the catecholamines---adrenaline, noradrenaline, and isoprenaline---on paper chromatograms was examined to determine the effect of numerous variables on R_f values. In general, R_f values depend on the grade of Whatman paper used and the temperature at which chromatography is run. The R_f values were markedly reduced on papers not washed or sprayed with acid, and these values fell with decreasing water content when miscible pairs of liquids were used as chromatographic solvents. Values obtained varied inversely with the distance the solvent traveled and with the number of times the solvent was used. The use of R_f values to locate and identify catecholamines on chromatographic paper is misleading since they are dependent on too many factors.

Chelsea College of Science and Technology
London, SW.3, England

1304 Worthen, L. R., Platiau, P. E., & Youngken, H. W., Jr. **The metabolism of 5-hydroxytryptamine in cultures of Claviceps purpurea.** (Letter) Journal of Pharmacy and Pharmacology, 15:626-627, 1963.

After 14 to 67 days growth of Claviceps purpurea, mycelial pads were separated from substrates, washed twice with 50 ml of saline, and drained. Twelve mg of 5HT creatinine sulfate in saline was added to the culture flask, which was then shaken at 20° to 25° C for 1 to 4 hours. Aliquots of the medium were analyzed for 5HT according to Udenfriend et al. An initial aliquot was analyzed just after adding the 5HT solution and analyses of subsequent aliquots were calculated as a percentage of the initial value. A marked loss of 5HT was noted in the medium of cultures of 21 to 67 days growth. Mycelia of similar age (16, 20, 29, 39 days) were separated from

culture substrates, frozen overnight, and allowed to thaw slowly. After homogenization, recovery of the supernatant, and incubation, the reaction mixtures were pooled, concentrated, and analyzed chromatographically by the methods of Matthias, using a descending strip method. Dried strips were sprayed with Ehrlich's reagent. The mycelial extract gave two intense blue flourescent spots, one of which had the same R_f value as the single spot given by the control and by a reference spot of 5HT creatinine sulfate. The second spot was not identified; the R_f value did not correspond with those of a number of indole reference compounds.

University of Rhode Island
Kingston, Rholde Island

1305 Bose, B. C. & Vijayvargiya, R. **Detection of tryptophan synthesising enzyme in Rauwolfia serpentina benth.** (Letter) Journal of Pharmacy and Pharmacology, 15:215, 1963.

Fresh homogenates of roots and leaves of Rauwolfia serpentina were prepared in M/15 phosphate buffer (pH 7.8), and the ratio of homogenate to buffer was adjusted to 1:2. Enzyme activity was determined by measuring the rate of disappéarance of indole and subsequent formation of tryptophan. Samples containing indole, serine, glutathione, pyridoxal phosphate, enzyme extract, and the buffer were incubated for 4 hours, and the unreacted free indole was extracted with toluene and estimated colorimetrically. Tryptophan concentrations were measured in the remaining aqueous liquid by the method of Nason et al. The amount of tryptophan formed corresponded to the quantity of indole used in the reaction. The presence of enzyme was confirmed by omitting serine and one of the substrates and adding sodium cyanide, an enzyme inhibitor. In the absence of serine, 5% indole was utilized, compared with 50% in the control experiments. There was practically no change in the indole content in the presence of sodium cyanide.

M.G.M. Medical College
Indore, India

1306 Brocklehurst, W. E. **"SRS-A". The slow reacting substance of anaphylaxis.** Biochemical Pharmacology, 12:431-435, 1963.

SRS-A is one of several pharmacologically active substances contributing to anaphylaxis. It is an acidic substance of small molecular size and is formed in sensitized tissue after that tissue is challenged by antigen. Present knowledge indicates that SRS-A is important in human asthma. The evidence concerning its pharmacological actions and the events by which it is formed in tissue are briefly reviewed.

Edinburgh University
Edinburgh, Scotland

1307 Roberts, D. J. **The influence of lipid on the paper chromatographic behaviour of sympathomimetic catecholamines in plasma extracts.** Journal of Pharmacy and Pharmacology, 15:579-583, 1963

An extraction technique to overcome displacement of the R_f values of catecholamines by lipid is described. Blood was collected from the femoral arteries of heparinized rabbits under urethane anesthesia. The plasma was removed and aliquots were mixed with a solution of noradrenaline, adrenaline, and isoprenaline in distilled water before preparation of an extract for chromatography by the methods of Vogt or Peacock or by the new method described. In this method, the plasma was shaken with six times its volume of cold acid-ethanol (1.0 ml hydrochloric acid/liter absolute ethanol) and left for 1 hour at -20° C. Following centrifugation, washing, and recentrifugation, the combined supernatants were distilled at 0.5 to 1.0 mm Hg (bath temperature 30° to 35° C). The moist residue was shaken with 4.0 ml ether-benzene mixture (5:2) plus 4.0 ml of 0.01 N hydrochloric acid. The flask was washed with more hydrochlic acid, and the total 10-ml volume was centrifuged at 3,000 rpm for 5 minutes. The clear, aqueous lower layer was mixed with an equal volume of absolute ethanol, saturated with sodium chloride, and redistilled. The residue was washed with acetone--ethanol (1:1), centrifuged, and the supernatant chromatographed on paper. This extraction method resulted in constant R_f values for the catecholamines. Blank activity between the spots was largely eliminated, biological assays were parallel, and the grease spots at the application areas were no longer evident.

Chelsea College of Science and Technology
London, England

1308 Hamberger, B., Norberg, K. -A., & Sjöqvist, F. **Evidence for adrenergic nerve terminals and synapses in sympathetic ganglia.** International Journal of Neuropharmacology, 2(6):279-282, 1963.

The findings of the author, published in 1963, that some norepinephrine is also present in nerve terminals are discussed in greater detail. Of 20 adult male and female cats, 17 were untreated and 3 were pretreated with reserpine (5 mg/kg i.p., 24 hours). The superior cervical stellate, fourth lumbar, seventh lumbar, first sacral, and prevertebral coeliac and inferior mesenteric ganglia were rapidly removed from the living anesthetized cat or immediately after death, and were prepared for fluorescence microscopy. A very prominent network of varicose nerve fibers with intense green to yellow--green fluorescence was found consistently in the prevertebral, and especially in the inferior mesenteric ganglia, but relatively few such fibers were found in other ganglia. These nerve fibers often terminated in close contact with fluorescent nerve cell bodies, sometimes completely surrounded by a "basket" of fluorescent fibers suggestive of synaptic structure. No specific fluorescence developed in ganglia after administration of reserpine, or when formaldehyde gas treatment was omitted in the microscopic preparation. That the fluorescent nerve fibers comprise synaptic adrenergic nerve terminals is strongly suggested by the following: morphologic similarity to conventional adrenergic nerve terminals in peripheral tissues; presence of abundant varicosities typical of nerve terminals in autonomic ganglia; and the "basket" arrangement of fluorescent nerve fibers around the ganglion cells, highly suggestive of the synaptic function of the transmitter.

Karolinska Institutet
Stockholm, Sweden

1309 Daniel, J. W. **The metabolism of ^{36}Cl-labelled trichloroethylene and tetrachloroethylene in the rat.** Biochemical Pharmacology, 12:795-802, 1963.

Synthesized Cl^{36}-labeled trichloroethylene and tetrachlorethylene were fed to Wistar rats (180 to 220 g in weight) by stomach tube; the percentage of radioactivity excreted in urine, feces, and expired air was measured; and the nature and amount of individual metabolites were determined. The specific activities of metabolic trichloroacetic acid and trichloroethanol were shown to be the same as that of the administered trichloroethylene, thus demonstrating an intramolecular rearrangement of chloride. About 15% of the dose of trichloroethylene was excreted in the urine. Tetrachloroethylene underwent little metabolism, and only 2% of the radioactivity was excreted in the urine. Both trichloroethylene and tetrachloroethylene are largely excreted through the lungs, although there is an appreciable difference between the rates of excretion of the two compounds. Tetrachloroethylene has no effect on the liver--lipid content of rats exposed to high concentrations (1,000 ppm) of the vapor. A scheme is presented that would account for the formation of the known metabolites of both trichloroethylene and tetrachloroethylene.

Imperial Chemical Industries Ltd.
Welwyn, Hertfordshire, England

1310 Lehr, H., Karlan, S. & Goldberg, M. W. **Substituted 3-thiomorpholinones.** Journal of Medicinal Chemistry, 6(2):136-141, 1963.

A series of 3-thiomorpholinones substituted in positions 2, 4, 5, or 6 were prepared and evaluated for possible hypnotic or sedative activity. Results indicated that only those 3-thiomorpholinones that had one or two alkyl groups in position 2 exhibited hypnotic activity. The most active compound was 2,2-diethyl-3-thiomorpholinone; in mice, it had an LD_{50} of 2,250 mg/kg, p.o. and 652 mg/kg, i.p. The HD_{50} was 750 mg/kg, p.o. and 166 mg/kg, i.p.; duration of hypnosis was 13 minutes p.o. and 7 minutes i.p. Of the sulfoxides and sulfones in the series, only 2,2-diethyl-3-thiomorpholinone 1,1-dioxide had hypnotic activity. In mice, it had an oral LD_{50} of 4,250 mg/kg and an oral HD_{50} of 1,250 mg/kg.

Hoffmann-LaRoche Inc.
Nutley, New Jersey

1311 Davis, M. A., Sunahara, F. A., Herr, F., & Gaudry, R. **New psychotropic agents. VI. Basic esters of 5-hydroxydibenzo[a,d]cycloheptadiene-5-carboxylic acid.** Journal of Medicinal Chemistry, 6(5):513-516, 1963.

Dibenzo[a,d]cycloheptadiene-5-carboxylates were synthesized and evaluated for pharma-

cological activity. The compounds were generally inactive as stimulants and antispasmodics.

Ayerst Research Laboratories
Montreal, Canada

1312 Krapcho, John. **Antispasmodics. II. α-Phenyl-α-substituted 2-pyridinebutanols and related compounds.** Journal of Medicinal Chemistry, 6(6):814-815, 1963.

A series of phenylpyridylalkyl ketones were prepared and converted to the corresponding tertiary alcohols or piperidyl alcohols for testing as antispasmodics. Of the variety of tertiary alcohols containing an unsubstituted phenyl group, the methobromide of the isopropyl derivative was the most active in controlling acetylcholine-induced spasms on the isolated rabbit ileum. The addition of a chlorine atom at the ortho position of the phenyl group produced a compound with antispasmodic activity equal to that of atropine. Activity was decreased by an ethyl group on the 5-position of pyridyl ring and by the introduction of a methylene group between the tertiary hydroxy group and the quaternary nitrogen. The methobromides of the phenylpiperidyl alcohols were less active than the corresponding pyridyl analogs.

Squibb Institute for Medical Research
New Brunswick, New Jersey

1313 Horrom, Bruce W. & Lynes, T. E. **The anticonvulsant properties of some substituted benzamides.** Journal of Medicinal Chemistry, 6(5):528-532, 1963.

Substituted aromatic amides were prepared for evaluation as anticonvulsants. Only 4-amino-N-cyclopropyl-3,5-dichlorobenzamide and its dibromo analog were effective in preventing convulsions produced by strychnine. The dichloro compound was also the most effective against pentamethylenetetrazol-induced convulsions. Activity was increased by N-alkyl substituents with maximum activity present when the cyclopropyl substituent was used. Protection against the lethal effects of pentamethylenetetrazol seemed to be correlated with protection from its convulsant effects. Electroshock seizures were antagonized by N-cyclopropyl-2,4-dichlorobenzamide and by 3-amino-N-cyclopropyl-2,5-dichlorobenzamide. The N-cyclopropyl substitution did not cause a decrease in activity, but any other change in this position markedly decreased potency.

Abbott Laboratories
North Chicago, Illinois

1314 Krapcho, John, Szabo, Attila, & Williams, June. **Synthesis of substituted 2-phenyl 1,4-benzothiazine 3(4H)-ones, and their activity as inhibitors of 1,4-dipyrrolidine-2-butyne.** Journal of Medicinal Chemistry, 6(2):214-216, 1963.

Substituted 2-phenyl-1,4-benzothiazin-3(4H)-ones were synthesized, and their activity as inhibitors of 1,4-dipyrrolidino-2-butyne was determined. Of the compounds tested, 4-(2-dimethylaminopropyl)-2-phenyl-1,4-benzothiazin-3(4H)-one was the most active. Other modifications of the basic side chain gave compounds of markedly decreased activity. Of the compounds containing substituents in either the nucleus or the 2-position of the phenyl ring, only the 4-chlorophenyl analog was highly active.

Squibb Institute for Medical Research
New Brunswick, New Jersey

1315 Burger, Alfred, Standridge, Robert T., & Ariens, E. J. **Cyclopropyl and cyclobutyl analogs of phenyl-substituted medicinal agents.** Journal of Medicinal Chemistry, 6(3)221-227, 1963.

Cyclobutyl analogs of the following phenyl-substituted drugs were synthesized for biological evaluation: phenobarbital, α-phenyl-N-methylsuccinimide, phenylbutazone, cinchophen, and 4-amino-2-phenylquinoline. When tested for motor activity effects in mice, 2-amino-1-cyclobutylpropane hydrogen succinate was inactive even after iproniazid pretreatment; cyclopentamine was as active as amphetamine. In tests for anesthetic potency, doses of 5-cyclobutyl-5-ethylbarbituric acid needed to produce anesthesia and to maintain sleeping time were about 50% of those of cyclobarbital. Cyclobutylalanine was a weak antagonist of leucine for E. coli and L. dextranicum.

University of Virginia
Charlottesville, Virginia

1316 Krapcho, John, Rubin, Bernard, Drungis, Anne M., Spitzmiller, Ervin R., Turk, Chester F., Williams, June, Craver, Bradford N., & Fried, Josef. **2'-(3-Dimethylamino-propylthio)cinnamanilide and related compounds: A new class of potent and relatively specific serotonin inhibitors.** Journal of Medicinal Chemistry, 6(2):219, 1963.

At concentrations ranging from 0.0005μg/ml, to 0.03μg/ml, 2'-(3-dimethylaminopropylthio) cinnamanilide (I) inhibited the spasmogenic effect of 0.2μg/ml of serotonin on the excised rat uterus. This corresponds to 157 times the antiserotonin activity of BAS, with a potency range of 60 to 407 times BAS at $p = 0.05$. Marked in vivo antiserotonin activity of the cinnamanilide was also demonstrated. The introduction of a chlorine atom into the ortho or para position of the cinnamoyl group gave compounds having activity similar to that of I. Replacement of the cinnamoyl moiety by dihydrocinnamoyl, benzoyl, or propionyl gave compounds with activity comparable to BSA. The oxygen analog of I was highly active, and a compound that contained only methylene groups in the side chain was moderately active.

Squibb Institute for Medical Research
New Brunswick, New Jersey

1317 Friedman, Orrie M., Parameswaran, K. N., & Burstein, Sumner. **Synthesis of phenethylamines related to mescaline as possible psychotomimetic agents.** Journal of Medicinal Chemistry, 6(3):227-229, 1963.

Compounds related to mescaline were prepared for biological evaluation. The acute toxicities and behavioral effects of β-hydroxymescaline hydrochloride (I), tetrahydroisoquinoline hydrochloride (II), and N-methyl-β-hydroxymescaline (III) were determined in male albino Swiss mice. The LD_{50} (i.p.) of mescaline is from 400 to 800 mg/kg; the three analogs had LD_{50}'s of 410, 520, and 440 mg/kg, respectively. Gross effects of these compounds ranged from ataxia, to fine tremors, to clonic convulsions. Compound II produced effects most like mescaline; the monomethyl compound was quite different in that it produced contraction of abdominal muscles and with hind leg rigidity. These compounds did not depress the spontaneous contractions of the isolated rabbit intestine.

Brandeis University
Waltham, Massachusetts

1318 Elison, Christian, Elliott, Henry W., Look, Melvin, & Rapoport, Henry. **Some aspects of the fate and relationship of the N-methyl group of morphine to its pharmacological activity.** Journal of Medicinal Chemistry, 6(3):237-246, 1963.

The chemical synthesis of N-trideuteriomethylnormorphine is described; it was found to be significantly less potent than morphine, although its duration of action was not affected by the isotope substitution. The labeled compound was demethylated less rapidly than morphine and required a larger energy of activation. Diminished capacity of the enzymes of tolerant rats to N-demethylate morphine was shown to be caused by the reduced availability of enzymes rather than by alteration in enzyme structure. Two methods were used to show that nalorphine inhibited the N-demethylation of morphine noncompetitively.

University of California Medical Center
San Francisco, California

1319 Finkelstein, Jacob, Romano, John A., Chiang, Elliot, & Lee, John. **Monoamine oxidase inhibitors. IV. Some dialkylaminophenylalkylhydrazines and related compounds.** Journal of Medicinal Chemistry, 6(2):152-155, 1963.

The syntheses 1-(4-dimethylaminocyclohexyl)-2-hydrazinopropane dihydrochloride (II) and 4-(4-dimethylaminophenyl)-2-butanone oxime (III) are reported. The compounds were tested for MAO activity in mice, using iproniazid and pheniprazine as reference standards. Both compounds had lower activity and/or higher toxicity than the reference materials.

Hoffmann-LaRoche Inc.
Nutley, New Jersey

1320 Davis, M. A., Winthrop, S[illegible]ley O., Stewart, J., Sunahara, F. A., & Herr, F. **New psychotropic agents. V. Derivatives of 5-cyano- and 5-carboxamidodibenzo[a,d]cycloheptadiene.** Journal of Medicinal Chemistry, 6(3):251-255, 1963.

Derivatives of 5-cyano- and 5-carboxamidodibenzo[a,d]cycloheptadiene were prepared and screened for pharmacological activity. In general, the compounds were less potent and less toxic than amitriptyline. None of the compounds were as effective as amitriptyline

in protecting against maximal electroshock seizures. The tertiary amines had antiacetylcholine activity that was less than 4% of that of atropine. Quaternarization of the amines increased antiacetylcholine activity. No significant antihistamine activity was observed.

Ayerst Research Laboratories
Montreal, Canada

1321 Leonard, F., Wajngurt, A., Klein, M., & Meyer, H. **Centrally active 2-(substituted phenyl)-γ-aminobutyric acids.** Journal of Medicinal Chemistry, 6(5):539-541, 1963.

A series of aminoalkylmalonates and GABA derivatives were prepared and screened for CNS effects and toxicity. All but one of the compounds were found to be short-acting central stimulants when administered in large doses. No additional pharmacological studies were performed.

Geigy Research Laboratories
Ardsley, New York

1322 Boissier, J. R., Ratouis, R., & Dumont, C. **Synthesis and pharmacological study of new piperazine derivatives.** Journal of Medicinal Chemistry, 6(5):542-544, 1963.

Twenty-three 1,4-disubstituted piperazines were prepared for biological screening. Three compounds showed marked adrenolytic activity: 1-(3,4-dimethoxybenzyl)-4-phenylpiperazine; 1-(3,4-dimethoxybenzyl)-4-(2-methoxyphenyl)piperazine: and 1-(3,4-dimethoxybenzyl)-4-(2-pyridyl)piperazine. All of the compounds showed weak and easily reversible antihistaminic activity.

Institut de Pharmacologie
Faculté de Médicine
Paris, France

1323 Krapcho, John, Spitzmiller, Ervin R., & Turk, Chester F. **Substituted 2,3-dihydro-1,5-benzothiazepin-4(5H)-ones and 3,4-dihydro-2-phenyl-(2H)-1,6-benzothiazocin-5(6H)-ones.** Journal of Medicinal Chemistry, 6(5):544-546, 1963.

The synthesis and alkylation of substituted 2,3-dihydro-1,5-benzothiazepin-4(5H)-ones are described. The preparation of 3,4-dihydro-2-phenyl-2H-1,6-benzothiazocin-5(6H)-one and of 6-(2-dimethylaminoethyl)-3,4-dihydro-2-phenyl-2H-1,6-benzothiazocin-5(6H)-one hydrochloride is also reported. Psychosedative activity was determined in rats with lesions in the septal area of the brain. Three compounds showed high activity. One compound, 2,3-dihydro-5-diethylaminoethyl-2-phenyl-1-5-benzodiazepine-4(5H)-one hydrochloride, was twice as potent as chlordiazepoxide when given i.p. This compound was also tested for ability to inhibit tremors produced by 1,4-dipyrrolidino-2-butyne, and was about one-third as active as 4-(2-diethylaminoethyl)-2-phenyl-1,4-benzothiazin-3(4H)-one hydrochloride, which showed no calming effect in the septal rat.

The Squibb Institute for Medical Research
New Brunswick, New Jersey

1324 Belleau B. & Cooper, P. **Conformation of N-(β-chloroethyl)-2-phenoxyethylamines in relation to adrenergic blocking activity.** Journal of Medicinal Chemistry, 6(5):579-583, 1963.

Previous rationalizations on the conformational requirements for adrenergic blocking activity of N-(β-chloroethyl)-2-phenoxyethylamines are briefly summarized. To test the validity of some earlier interpretations, the synthesis of cis- and trans-cyclopentane analogs of this class of blocking agents was accomplished. The new alkylating agents N-methyl-N-(β-chloroethyl)-cis-2-phenoxycyclopentylamine HCl and N-methyl-N-(β-chloroethyl)-trans-2-phenoxycyclopentylamine HCl are highly active adrenergic blocking agents, surpassing the parent compound by a factor of about 100. Conformational properties of the new drugs are discussed.

University of Ottawa
Ottawa, Ontario, Canada

1325 McColl, J. D., Chubb, F. L., Lee, C. F., Hajdu, A., & Komlossy. **Synthesis and pharmacological properties of phenyl-substituted biurets.** Journal of Medicinal Chemistry, 6(5):584-587, 1963.

A series of phenyl-substituted biurets was synthesized and tested for their effect on gastric secretion and on the inhibition of ulcer formation in the pyloric ligated rat; the anticonvulsant profile of these compounds was also investigated. The LD50's

were determined i.p. by the method of Litchfield and Wilcoxon. Injection of the compounds produced ataxia, depression followed by loss of righting reflex, paralysis, and at higher dose levels, vasodilatation. In general, increasing the length of the alkyl substituents resulted in a decrease in toxicity. Phenethylbiuret and phenpropylbiuret were the most effective agents. Since phenethylbiuret was the most active agent against ulcer formation and as an anticonvulsant, it was tested further for pharmacological properties in the cat, rat, and mouse. Phenethylbiuret did not possess any anticholinergic or antispasmodic activity. It was shown to inhibit both polysynaptic and monosynaptic pathways, to inhibit conditioned avoidance response in the rat, and to potentiate hexobarbital and ether-induced loss of righting reflex. Compared to other CNS agents, phenethylbiuret was relatively weak as a central depressant.

Frank W. Horner Limited
Montreal, Quebec, Canada

1326 Howell, Hilda, Pollard, C. B., Kier, Lemont B., & Sisler, Harry H. **Derivatives of 1-phenyl-4-(2-hydroxy-3-methoxypropyl)piperazine.** Journal of Medicinal Chemistry, 6(5):604-607, 1963.

The preparation and characterization of derivatives of 1-phenyl-4-(2-hydroxy-3-methoxypropyl)piperazine and the synthesis of four 1-aryl-4-(2-hydroxy-3-methoxypropyl)piperazines and their use in the preparation of the respective methyl ethers are described. The compounds were evaluated pharmacologically. A slight-to-moderate adrenergic blocking action was seen with 1-phenyl-4-(2-methoxycarbonyloxy-3-methoxypropyl)piperazine, 1-phenyl-4-(2-ethoxy-3-methoxypropyl)piperazine, and 1-phenyl-4-(2-benzyloxy-3-methoxypropyl)piperazine when tested for the reversal of epinephrine effect on blood pressure in vivo; 1-phenyl-4-(2-methoxycarbonyloxy-3-methoxypropyl)piperazine also showed moderate hypotensive activity. A moderate cerebral depressant activity was seen with 1-(2-ethoxy)phenyl-4-(2-hydroxy-3-methoxypropyl)piperazine and 1-(2-n-propylthio)phenyl-4-(2-hydroxy-3-methoxypropyl)piperazine when tested as antiexcitants in rats.

University of Florida
Gainesville, Florida

1327 Benigni, J. D. & Verbiscar, Anthony J. **The synthesis of two new metabolites of catecholamines: 3,4-Dihydroxyphenylethyleneglycol and 4-hydroxy-3-methoxyphenylethyleneglycol.** Journal of Medicinal Chemistry, 6(5):607-608, 1963.

Two metabolites of epinephrine and norepinephrine, 4-hydroxy-3-methoxyphenylethyleneglycol and 3,4-dihydroxyphenylethyleneglycol, were prepared to complete their identification by chemical syntheses. Pharmacological properties are not reported.

Regis Chemical Company
Chicago, Illinois

1328 Poos, George I., Carson, John R., Rosenau, Janet D., Roszkowski, Adolph P., Kelley, Nancy M., & McGowin, Janet. **2-Amino-5-aryl-2-oxazolines. Potent new anorectic agents.** Journal of Medicinal Chemistry, 6(3):266-272, 1963.

A series of 2-amino-5-aryl-2-oxazolines was found to have potent appetite-suppressant activity. Methods of synthesis and chemical behavior for these compounds are described. Anorectic activity was determined by the compound's ability, after p.o. administration in rats, to inhibit the consumption of beef broth. Because of the effect of optical isomersism on the anorectic activity of the amphetamines, several isomers of 2-amino-4-methyl-5-phenyl-2-oxazoline were examined for effect on anorectic activity. The trans form and the dextrorotatory form were found to have about the same potency as the cis form. Structure--activity relationships are discussed in detail. The CNS activity, cardiovascular effects, and anorectic activity all vary significantly with changes in structure.

McNeil Laboratories, Inc.
Fort Washington, Pennsylvania

1329 Wright, W. B., Jr. & Hardy, R. A., Jr. **Synthetic analgesics. IV. Synthesis of enantiomers of basic anilides containing the phenalkyl moiety.** Journal of Medicinal Chemistry, 6(2):128-130, 1963.

The enantiomers of N-[2-(methylphenethylamino)propyl]propionanilide sulfate, diampromide, and N-[2-(benzylmethylamino)propyl]propionanilide hydrochloride were prepared. The compounds were tested for analgesic activity by the rat-tail radiant-heat-

procedure of Osterberg and Rauh. The activities of the racemates and enantiomers are tabulated. One enantiomer of each pair greatly exceeds the other in analgesic activity, and the more active enantiomers have the same configuration.

Lederle Laboratories
Pearl River, New York

1330 Kase, Yoshitoshi, Yuizono, Tomokazu, & Muto, Mieko. **Piperidino groups in antitussive activity.** Journal of Medicinal Chemistry, 6(2):118, 1963.

This paper describes the antitussive activities obtained with 73 compounds in five groups: analgesics, antitussives in the phenothiazine series, adrenergic amines, antihistaminics, and camphor derivatives. The effects were evaluated by Kasé's method in unanesthetized dogs and/or in slightly pentobarbitalized cats, using 20 mg/kg of compound i.p. The antitussive effects of each test drug was determined from the decreases in both amplitude and frequency of cough curves and from the duration of such an effect. The effective dose was that necessary to decrease amplitude and/or frequency of coughing by more than 20%, as compared with the control, and to prolong the effect for more than 20 minutes. Each drug of the same group was evaluated in the same group of animals, thereby minimizing errors of individual differences. The antitussive activities of piperidino compounds were the highest of all the amino compounds tested, in spite of differences of stimulation or species. The hypothesis that the introduction of a piperidino group into a compound showing any actions on the CNS can produce antitussive activity was thus consolidated as a guide for further studies on antitussive agents.

University of Kumamoto
Kumamoto, Japan

1331 Winthrop, Stanley O., Davis, M. A., Herr, F., Stewart, J., & Gaudry, Roger. **New psychotropic agents. IV. Derivatives of dibenzo[a,d][1,4]cyclooctadiene.** Journal of Medicinal Chemistry, 6(2):130-132, 1963.

A series of 5-dialkylaminoalkyl-5-hydroxydibenzo[a,d][1,4]cycloöctadienes was prepared by treating dibenzo[a,d][1,4]cycloöctadien-5-one with basically substituted Grignard reagents. The corresponding 5-dialkylaminoalkyl- and 5-dialkylaminoalkylidenedibenzo[a,d][1,4]cycloöctadienes also were synthesized. Pharmacological activity was determined by the following tests: LD_{50}, potentiation of a subhypnotic dose of ethanol, protection against maximal electroshock seizures (MES), mydriatic action, depression of orientational hypermotility, ataxic effect, and influence on a conditioned response (runway test). The compounds were further tested for ability to inhibit contractions induced by acetylcholine and histamine in isolated guinea-pig ileum. Results are tabulated, and for comparison, data obtained for amitriptyline are also included. Several of the compounds exhibited central and peripheral pharmacological activities similar to amitriptyline and other dibenzo[a,d][1,4]cycloheptadiene compounds. In general, they were less potent centrally than amitriptyline and had less pronounced mydriatic effects.

Ayerst Research Laboratories
Montreal, Quebec, Canada

1332 Freifelder, Morris. **N-alicyclic amphetamines.** Journal of Medicinal Chemistry, 6(6):813, 1963.

Several N-alicyclic amphetamines were prepared and tested as appetite depressants. The cyclopropyl derivative was active, but the cyclobutyl derivative had only slight activity; all others in the series were inactive.

Abbott Laboratories
North Chicago, Illinois

1333 Gal, Andrew E. & Avakian, Souren. **Nitrogen substituted phenoxazines.** Journal of Medicinal Chemistry, 6(6):809-811, 1963.

A number of 10-substituted phenoxazines were synthesized for biological testing. Three compounds decreased the mean arterial blood pressure of dogs anesthetized with pentobarbital: 10-[(1-pyrrolidyl)acetyl]phenoxazine hydrochloride (I, 70% decrease); 10-(2-dimethylaminopropionyl)phenoxazine hydrochloride (II, 60% decrease); and II as the methiodide (III, 36% decrease). The hypotensive activity of all three compounds was of short duration, returning to control level in less than 15 minutes. When tested for anticholinergic and spasmolytic activity, compound I, in a concentration of 1 to 5 X 10^{-5}, inhibited barium chloride-induced spasms by 19%. In a concentration of 1 to 2

X 10^{-7}, it inhibited acetylcholine-induced spasms by 10%. Compound II inhibited barium chloride-induced spasms by 30% in a concentration of 1 to 2.5 X 10^{-7}. At a concentration of 1 to 2.5 X 10^{-7}, compound III inhibited barium chloride-induced spasms by 40% and histamine-induced spasms by 30%. At 1 to 2.5 X 10^{-8}, it inhibited acetylcholine-induced spasms by 20%.

The National Drug Company
Philadelphia, Pennsylvania

1334 Sternback, L. H., Fryer, R. Ian, Keller, O., Metlesics, W., Sach G., & Steiger, N. **Quinazolines and 1,4-benzodiazepines. X. Nitro-substituted 5-phenyl-1,4-benzodiazepine derivatives.** Journal of Medicinal Chemistry, 6(3):261-265, 1963.

A series of 1,3-dihydro-5-phenyl-2H-1,4-benzodiazepin-2-ones with nitro groups on the nucleus and the 5-phenyl substituent were prepared, and three compounds were evaluated as psychotherapeutic agents. These compounds showed a low toxicity combined with sedative, muscle relaxant, and anticonvulsant properties: 1,3-dihydro-7-nitro-5-phenyl-2H-1,4-benzodiazepin-2-one (I); 2-amino-7-nitro-5-phenyl-3H-1,4-benzodiazepine 4-oxide; and 2-methylamino-7-nitro-5-phenyl-3H-1,4-benzodiazepine 4-oxide. As a sedative and muscle relaxant, compound I was 7 times as active in mice and 20 times as active in cats as was chlordiazepoxide.

Hoffmann-LaRoche Inc.
Nutley, New Jersey

1335 Hayao, Shin, Schut, R. N., & Stryc-ker, W. G. **New sedative and hypotensive phenylpiperazine esters and carbamates.** Journal of Medicinal Chemistry, 6(2):133-135, 1963.

A number of polymethoxybenzoates and N-substituted carbamates of 4-aryl-1-piperazylalkanols were synthesized for testing as potential sedative agents. Many of the compounds had antiadrenergic activity. After i.v. administration, they reversed or blocked the pressor response to epinephrine and partially blocked the response to norepinephrine. In anesthetized dogs, i.v. doses produced sustained hypotension; in unanesthetized dogs, the effect of orally administered drugs was uncertain and variable. When the esters were screened for sedative activity, 4-(4-phenyl-1-piperazyl)butyl 3,4,5-trimethoxybenzoate dihydrochloride was the most active. Its median oral sedative dose was 4% of the average LD_{50} (100 mg/kg). In the carbamate series, 4-phenyl-1-[2-3,4,5-trimethoxyphenylcarbamoyloxy)propyl]-piperazine produced minimal sedative effects at 27 mg/kg (3% of the average LD_{50}) in rats. At 36 mg/kg i.p., this compound gave 100% protection against d-amphetamine sulfate (15 mg/kg, i.p.) toxicity in grouped mice.

Miles Laboratories, Inc.
Elkhart, Indiana

1336 Monroe, A. M., Quinton, R. M., & Wrigley, T. I. **Some analogs of imipramine.** Journal of Medicinal Chemistry, 6(3):255-261, 1963.

Dialkylaminoalkyl derivatives of 5,6,11,12-tetrahydrodibenz[b,f]azocine, 5-amino-10,11-dihydro-5H-dibenzo[a,d]cycloheptene, and 10,11-dihydro-5H-dibenzo[b,e][1,4]diazepine were synthesized. In tests for autonomic activity and antagonism of reserpine effects, the N-(3-dimethylaminopropyl) derivatives of the first two ring systems showed negligible activity, whereas 5-(3-dimethylaminopropyl)-10,11-dihydrodibenzo[b,e][1,4]diazepine showed activity comparable to that of imipramine. However, when the benzodiazepine derivative was given to dogs, cats, or monkeys in doses about double those necessary to antagonize certain reserpine effects, it induced convulsions. In dogs and cats, repeated doses gave rise to leucocytopenia and liver damage. The monomethylaminopropyl derivatives of the first two ring systems and of desmethylimipramine had greater potency than their dimethyl homologs in the tests for antagonism to reserpine and potentiation of adrenergic agents, but less sympatholytic and parasympatholytic properties.

Pfizer Ltd.
Kent, England

1337 Kalir, Asher & Szara, Stephen. **Synthesis and pharmacological activity of fluorinated tryptamine derivatives.** Journal of Medicinal Chemistry, 6(6):716-719, 1963.

Several fluorinated tryptamine derivatives were prepared. The 5-fluoro and unsubstituted tryptamines were more active than the 6-substituted derivatives in inducing spontaneous locomotion when administered to reserpinized white mice. The effect of 6-fluorodiethyltryptamine was compared with diethyltryptamine (DET) in six patients and one normal volunteer. After a 1 mg/kg, i.m.

dose, DET produced sympathomimetic autonomic symptoms, perceptual disturbances, hallucinations, mood changes, and difficulties in thinking and speaking. At the same dose, the 6-fluoro analog produced the autonomic symptoms and mood changes without the perceptual and thinking disturbances characteristic of hallucinogenic drugs. The urine of patients treated with DET contained various amounts of 6-hydroxy-DET. The urine of patients who received the 6-fluoro analog contained large amounts of the unchanged compound, but no 6-hydroxy derivative was detected.

Saint Elizabeths Hospital
Washington, D.C.

1338 Villani, Frank J., King, Mary S., & Villani, Florence J. **The chemistry of the benzylpyridines. V. β-phenyl-β-pyridyl-β-hydroxypropionic acids and derivatives as antispasmodic agents.** Journal of Medicinal Chemistry, 6(2):142, 1963.

The Reformatsky transformation was employed in obtaining ethyl β-phenyl-β-pyridyl-β-hydroxypropionates with possible pharmacological action from 2-, 3-, and 4-benzoylpyridine and the corresponding N-methylated 3- and 4-benzoylpiperidines. The $C_6H_5C(OH)RCH_2COOR$ and $C_6H_5CR{=}CHCOOH$ derivative groups are related to the series of potent antispasmodic and antihistaminic tertiary carbinols $C_6H_5CR(OH)CH_2CH_2NR'_2$, and their unsaturated derivatives of the $C_6H_5CR{=}CHCH_2NR'_2$ group. The general Reformatsky, general saponification, and catalytic hydrogenation procedures used are described. The melting point, C, H, and N content of the 13 compounds obtained were determined. These compounds were subjected to a variety of pharmacological screening procedures, showing that in general, the compounds had little biological activity. When given to rats p.o., β-phenyl-β-(2 piperidyl)-β-hydroxypropionic acid, 1-keto-3-phenyl-3-hydroxyoctahydroindolizine and ethyl β-phenyl-β-(3 piperidyl)-propionate showed some activity in the maximal electroshock procedure at doses of 180, 220, and 230 mg/kg, respectively, and had approximately 1.9, 1.6, and 1.5 times the activity of trimethadione. Ethyl β-phenyl-β-(3 piperidyl)-propionate had an oral in vivo antispasmodic activity equal to six-sevenths that of atropine sulfate, but it was toxic at this dosage.

Schering Corporation
Bloomfield, New Jersey

1339 von Strandtmann, Maximilian, Cohen, Marvin P., & Shavel, John, Jr. **Acyltryptamines. II. Synthesis of acyltryptamines, indazoles, and azepinoindoles from the acylphenylhydrazones of 2,3-piperidinedione.** Journal of Medicinal Chemistry, 6(6):719-725, 1963.

Tryptamines, 2-carbethoxytryptamines, azepino[5,4,3-cd]indoles, and 2H-indazoles were synthesized and examined for biological activity. In the preliminary acute-toxicity behavioral screen in mice, the carbethoxytryptamines and the indazoles failed to produce significant effects. Both types were relatively nontoxic. The azepinoindoles induced clonic--tonic convulsions and Straub tail. The ALD_{50} of the methyl compound was 75 mg/kg; that of the phenyl compound was 400 mg/kg. The 5-acyltryptamines showed antiserotonin and hypotensive activity. The most potent compound, 5-acetyltryptamine, produced a depressor response of 39 mm mercury at 0.025 mg/kg i.v. A dose of 0.25 mg/kg caused a drop in blood pressure of 61 mm that required 25 minutes to return to normal. Doses up to 5 mg/kg did not markedly enhance the hypotensive effect. The drug appeared to have no autonomic activity. Hypotensive effects were not evident when the drug was evaluated in a clinical trial. The hypotensive activity of 5-acyltryptamines decreased with increased size of the acyl group. The cycloanhydro derivatives of 4-acetyltryptamine and of 6-acetyltryptamine produced hypertensive effects.

Warner-Lambert Research Institute
Morris Plains, New Jersey

1340 Corrodi, H., Perrson, H., Carlsson, A., & Roberts, J. **A new series of substances which block the adrengeric β-receptors.** Journal of Medicinal Chemistry, 6(6):751-755, 1963.

A series of phenylethanolamines and phenylpropanolamines with chlorine or alkyl substitution in the benzene nucleus, and which block adrenergic β-receptors in mammals, was synthesized. A clear relationship between structure and activity allowed synthesis of potent β-receptor blocking agents with and without intrinsic sympathomimetic activity. In all the pharmacological screening procedures, dideoxydichloroisoproterenol (DCI) and nethalide, known β-receptor blocking agents, were used as reference compounds. All potential β-receptor blocking agents were tested on isolated rabbit heart for sympathomimetic activity

and for reduction in response to isoproterenol. The β-receptor blocking activity was estimated in isolated rabbit-heart papillary muscles. Antiarrhythmic properties were evaluated in cats against arrhythmias induced by the combined action of epinephrine and vagal stimulation ("vagus--amine" test). The screening results are tabulated. Structure--activity relationships are discussed in detail.

Research Laboratories AB Hässle
Göteborg, Sweden

1341 Yale, Harry L., Cohen, Allen I., & Sowinski, Francis. **Esters of 4-{3-[2-(trifluoromethyl)phenothiazin-10-yl]-1-piperazineëthanol as long-acting tranquilizing agents. Synthesis of 4-{3-[2-(trifluoromethyl)-phenothiazin-10-yl]propyl}-1-piperazineëthanol-ethyl-C^{14} and its ester with heptanoic acid. III.** Journal of Medicinal Chemistry, 6(4):347-350, 1963.

A number of esters of 4-{3-[2-(trifluoromethyl)phenothiazin-10-yl]propyl}-1-piperazineëthanol were prepared. The heptanoate, at 5% in sesame oil and injected s.c. as a depot, in doses 4 to 16 times above the ED_{100}, produced 50% to 100% inhibition (electric shock avoidance) for a minimum of 12 to 15 days. When the same concentration of the heptanoate in oil was given s.c. to dogs, it elevated their thresholds to the emetic action of apomorphine 32-fold for 4 weeks. The thresholds gradually returned to predose levels during a 3-week period. The metabolism and distribution of the C^{14}-labeled compounds were also studied.

The Squibb Institute for Medical Research
New Brunswick, New Jersey

See also: 1068, 1069, 1108, 1116, 1157, 1158, 1162, 1206, 1211, 1212, 1214, 1218, 1219, 1221, 1223, 1232, 1233, 1239, 1240, 1242, 1245, 1246

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